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OF

# DISEASES OF CHILDREN

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VOLUME VI  
1913

210782  
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PUBLISHERS  
AMERICAN MEDICAL ASSOCIATION  
CHICAGO, ILL.



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## CONTENTS VOLUME VI

### JULY, 1913. NUMBER 1

	PAGE
THREE TYPES OF OCCLUSION OF THE ESOPHAGUS IN EARLY LIFE. THOMAS MORGAN ROTCH, M.D., BOSTON.....	1
THE INFLUENCE OF ACTIVITY ON THE METABOLISM OF THE CHILD. PROF. DR. ARTUR SCHLOSSMANN AND DR. PHIL. HANS MURCHHAUSER, DÜSSELDORF	15
IS DIPHTHERIA FREQUENTLY A BACTERIEMIA? MATTHIAS NICOLL, JR., M.D., AND HARRIET L. WILCOX, NEW YORK.....	23
SIMPLE SYRINGE TRANSFUSION WITH SPECIAL CANNULAS. EDWARD LINDEMAN, M.D., BELLEVUE HOSPITAL, NEW YORK.....	28
A FORMULA FOR THE DETERMINATION OF THE SURFACE AREA OF INFANTS. JOHN HOWLAND, M.D., BALTIMORE, AND RICHARD T. DANA, PH.B., NEW YORK .....	33
PROGRESS IN PEDIATRICS: THE DIAGNOSIS AND TREATMENT OF ENLARGED THYMUS. ALFRED FRIEDLANDER, M.D., CINCINNATI.....	38
INDEX TO CURRENT PEDIATRIC LITERATURE.....	57

### AUGUST, 1913 NUMBER 2

PANCREATIC INSUFFICIENCY. LANGLEY PORTER, M.D., SAN FRANCISCO....	65
STATUS THYMOLYMPHATICUS, WITH REPORT OF FOUR CASES IN ONE FAMILY. WALTER L. BIERRING, M.D., J. A. GOODRICH, M.D., AND D. J. GLOMSET, M.D., DES MOINES, IOWA.....	75
NEEDLE IN THE HEART FIFTEEN MONTHS; DEATH; AUTOPSY. W. P. NORTHRUP, M.D., NEW YORK.....	87
THE DIAGNOSIS OF INTUSSUSCEPTION BY X-RAY. IRVING M. SNOW, M.D. AND MARSHALL CLINTON, M.D., BUFFALO, N. Y.....	93
MUCOUS CYST OF THE CECUM IN AN INFANT TEN WEEKS OLD, PRODUCING OBSTRUCTION OF THE ILEOCECAL VALVE AND SYMPTOMS SIMULATING AN INTUSSUSCEPTION. A. D. BLACKADER, M.D., MONTREAL.....	99
CARDIAC DISEASE IN CHILDHOOD, WITH SPECIAL REFERENCE TO PROGNOSIS. CHAS. HUNTER DUNN, M.D., BOSTON.....	104
THE DIAGNOSIS AND TREATMENT OF PYELITIS IN INFANCY. ROWLAND G. FREEMAN, M.D., NEW YORK.....	117
ANALYSIS OF ONE THOUSAND CASES OF EPIDEMIC MEASLES. C. V. CRASTER, M.D., ROSEBANK, N. Y.....	122
PROGRESS IN PEDIATRICS: RÉSUMÉ ON THE CIRCULATORY SYSTEM. J. HERBERT YOUNG, M.D., NEWTON, MASS.....	131
INDEX TO CURRENT PEDIATRIC LITERATURE.....	137

### SEPTEMBER, 1913. NUMBER 3

DYSPIUITARISM. MARK S. REUBEN, M.D., NEW YORK.....	145
A STUDY OF THE WASSERMANN REACTION IN ONE HUNDRED INFANTS. KENNETH D. BLACKFAN, M.D., S. T. NICHOLSON, JR., M.D., BALTIMORE, AND T. WISTAR WHITE, M.D., ST. LOUIS.....	162
THE WASSERMANN REACTION IN HEREDITARY SYPHILIS, IN CONGENITAL DEFORMITIES AND IN VARIOUS OTHER CONDITIONS IN INFANCY. L. E. HOLT, M.D., NEW YORK, N. Y.....	166
THE LUTIN REACTION IN INFANCY. ALAN BROWN, M.D., NEW YORK, N. Y.	171
RESULTS WITH SALVARSAN IN HEREDITARY SYPHILIS. L. E. HOLT, M.D., AND ALAN BROWN, M.D., NEW YORK.....	174



# CONTENTS OF VOLUME VI

	PAGE
RESULTS OF TREATMENT WITH SALVARSAN IN LATE CONGENITAL SYPHILIS. GEO. S. STRATHY, M.D., AND GEO. A. CAMPBELL, TORONTO.....	187
A RAPID CLINICAL METHOD FOR THE ESTIMATION OF TOTAL FAT IN INFANTS' STOOLS. D. M. COWIE, M.D., AND W. S. HUBBARD, PH.D., ANN ARBOR, MICH. ....	192
PROGRESS IN PEDIATRICS. RÉSUMÉ OF THE RECENT LITERATURE ON MEN- INGITIS (NOT INCLUDING MENINGOCOCCUS MENINGITIS). HENRY HEIMAN, M.D., AND SAMUEL FELDSTEIN, M.D., NEW YORK.....	199
INDEX TO CURRENT PEDIATRIC LITERATURE.....	215

## OCTOBER, 1913. NUMBER 4

THE CELL CONTENT OF MILK. D. M. LEWIS, M.D., NEW HAVEN, CONN.....	225
THE FURTHER STUDY OF THE ANATOMY AND PHYSIOLOGY OF THE INFANT STOMACH BASED ON SERIAL ROENTGENOGRAMS. GODFREY R. PISEK, M.D., AND LEON THEODORE LEWALD, M.D., NEW YORK.....	232
URINARY LITHIASIS IN INFANCY. ARTHUR N. COLLINS, A.B., M.D., DULUTH, MINN. ....	245
THE GASTRIC SECRETION OF INFANTS AT BIRTH. ALFRED F. HESS, M.D., NEW YORK .....	264
PROGRESS IN PEDIATRICS. REVIEW OF THE LITERATURE ON NOSE AND THROAT WITH REFERENCE TO CHILDREN. D. BRADEN KYLE, M.D., PHILADELPHIA, PA. ....	277
INDEX TO CURRENT PEDIATRIC LITERATURE.....	285

## NOVEMBER, 1913. NUMBER 5

HEAT AND SUMMER DIARRHEA. JOHN ZAHORSKY, M.D., ST. LOUIS.....	289
THE INFLUENCE OF ATMOSPHERIC CONDITIONS ON THE MORTALITY OF INFANTS SUFFERING WITH GASTRO-INTESTINAL DISORDERS. A. S. BLEYER, M.D., ST. LOUIS.....	319
THE COMPLEMENT-FIXATION REACTION OF THE BLOOD OF CHILDREN AND INFANTS, USING THE BACILLUS ABORTUS AS ANTIGEN. W. P. LARSON, M.D., AND J. P. SEDGWICK, M.D., MINNEAPOLIS.....	326
AN EXPERIMENT WITH RAW AND HEATED COW'S MILK AND ITS LESSON. WITH COMMENTS ON BACILLUS ABORTUS. E. C. SCHROEDER, M.D., BETHESDA, MD.....	334
THE ROENTGEN RAY IN PYLORIC OBSTRUCTION. L. R. DE BUYS, M.D., NEW ORLEANS, LA.....	344
VULVOVAGINITIS IN CHILDREN. RICHARD M. SMITH, M.D., BOSTON.....	355
PROGRESS IN PEDIATRICS. RÉSUMÉ OF THE LITERATURE ON THE EAR. S. MAC CUE SMITH, M.D., PHILADELPHIA.....	363
INDEX TO CURRENT PEDIATRIC LITERATURE.....	372

## DECEMBER, 1913. NUMBER 6

DUODENAL ULCERS IN INFANCY. L. EMMETT HOLT, M.D., NEW YORK.....	381
CASEIN IN INFANT FEEDING. EXPERIMENTS IN EXACT PERCENTAGES. HENRY I. BOWDITCH, M.D., AND A. W. BOSWORTH, A.M., BOSTON.....	394
PAROTITIS COMPLICATED WITH MENINGITIS. GEORGE N. ACKER, M.D., WASH- INGTON, D. C. ....	399
A CASE OF CONGENITAL CYST OF THE THYROID GLAND IN A CHILD AGED ONE YEAR, PRODUCING DEATH BY ASPHYXIATION. H. C. CLARK, M.D., ANCON; C. Z. AND ALFRED G. FARMER, M.D., GATUN, C. Z.....	408
PROGRESS IN PEDIATRICS. A REVIEW OF RECENT WORK ON MEASLES. WIL- LIAM PALMER LUCAS, M.D., SAN FRANCISCO.....	412
INDEX TO CURRENT PEDIATRIC LITERATURE.....	440



# American Journal of Diseases of Children

VOL. 6

JULY, 1913

No. 1

## THREE TYPES OF OCCLUSION OF THE ESOPHAGUS IN EARLY LIFE \*

THOMAS MORGAN ROTCH, M.D.

BOSTON

The following cases of occlusion of the esophagus of non-traumatic origin have been under my care in the wards of the Children's Hospital. The rather unusual occurrence of the condition in my experience and the importance of recognizing which type we are dealing with, on account of prognosis and treatment, are my reasons for reporting them. Considering the rarity of the condition it is to be noted as a coincidence that during Dr. Morse's service, preceding mine, three cases of esophageal narrowing entered the same wards and have been reported by him.

CASE 1.—The first case is that of a boy 25 months old. The labor was normal and the infant was normally developed. He was fed on breast milk for the first seventeen months. From birth he had always vomited, from four to six times daily. The vomiting had always occurred during the feedings and was never forcible. The child gagged or coughed a little and a considerable amount of the feeding would come out of his mouth. Sometimes he vomited just as he began his feeding and the amount then was a great deal more than he had just swallowed. The vomitus consisted of unchanged milk, not curdled or sour, and had no regular relation to the feedings. Sometimes he would retain several feedings and then vomit during the next two or three. He not only vomited breast milk but modifications of cow's milk. He seemed to be always hungry and had to be fed at least twelve times a day. It was found that he vomited less if he had only three ounces given at a feeding. He had always been constipated and he soon became a pale, thin baby.

Physical examination, beginning with the mouth and throat, was negative except for the heart, which was found to be decidedly dislocated to the right, and there was a blowing, systolic murmur, loudest at the base and transmitted to the left axilla. There was no systolic retraction. The urine was normal. Listening with a stethoscope over the epigastrium, when the child was swallowing, a slight splashing sound was heard fifteen to twenty seconds after the mouthful of milk had been swallowed. The sound was like that of a metallic trickling as though the milk came into the stomach by drops. The usual time for liquid to pass into the stomach at this age is five seconds.

A bismuth meal was given and a Roentgen examination immediately made. This showed a narrowing of the lower third of the esophagus extending not quite to the cardia. The esophagus was shown to be a little to the right of the median line and there appeared to be pericardial and mediastinal adhesions. The esophagoscope showed a stricture of the esophagus about 17 cm. from the incisor

\*Read at the meeting of the American Pediatric Society, Washington, D. C., May, 1913.

teeth, approached by a funnel-shaped narrowing while the upper part of the esophagus was found to be slightly dilated. The narrowing appeared very great and a sound,  $\frac{1}{4}$  cm. in diameter, could not be introduced. It may be said here that the distance from the gums to the cardia in the newborn is about 17 cm. and at three years from 23 to 24 cm. Figures 1, 2 and 3 show the stricture and 2 and 3 show that a certain amount of the bismuth meal had trickled through into the stomach. The child lost rapidly in weight and strength and the stricture was so small that it was deemed dangerous and therefore inadvisable by Dr. D. Crosby Greene to attempt to dilate it through the esophagoscope by the usual means. I might say in passing that in congenital cases, of which type this seemed to be, there is apt to be increased connective tissue around the esophagus which may extend down and form adhesions and thus displace the heart. It was these adhesions which were supposed to have caused the dislocation of the heart to the right. The only means of saving the child's life appeared to be a gastrectomy which would permit of the child's being fed directly into the stomach, and it was thought that when the general condition improved he might be able to stand the manipulation necessary to dilate the esophagus. The operation was performed but the child died. No autopsy was permitted.

This case represents an extreme congenital organic condition of a type which as a rule is inoperable and is almost universally fatal.

CASE 2.—The second case is a more favorable type for treatment and for life. This case represents a type of probable congenital narrowing not necessarily, however, of organic lesion in the esophagus but caused by congenital central spasm, resulting in dilatation of the esophagus above the point of narrowing. A girl of 10 years old, normal at birth, was fed on breast milk for eleven months and during this time was well and strong. She was then given cow's milk and cereals and at once began to vomit regularly during her meals. She would vomit several times while taking her food. The amount vomited was small, never more than a few mouthfuls. The vomiting caused her a good deal of effort and distress until she learned to aid its occurrence by putting her fingers down her throat. This continued until she was 4 years old and she had become a thin, pale, constipated child. At this time she swallowed a piece of meat in her soup and for four days following she vomited everything, even water. The vomiting then gradually lessened and she was kept on a diet of milk and cereals for two years. Since that time she had developed well and had become a strong, well girl. There was no history of her having swallowed anything corrosive. Four days before she was seen at the hospital she ate an orange and an hour later she was unable to eat her dinner because of discomfort which was only relieved by inducing vomiting with her fingers. She was unable to swallow anything, even water, without having to vomit it directly. She was in a very weak condition.

Nothing abnormal was found on physical examination. A bismuth meal was given and a Roentgen picture showed that the bismuth had passed only a little way beyond the middle of the esophagus, as shown in Fig. 4, and that there was none in the stomach. The part of the esophagus containing the bismuth was shown to be greatly dilated and at the bottom of this dilatation a circular object was made out the size of a small coin. An oval esophagoscope  $1\frac{1}{2}$  by 1 inch in diameter was passed into the esophagus by Dr. Greene and encountered a mass of orange pulp mixed with the bismuth. This was withdrawn and was found to be practically the whole of an orange pulp. Entangled in it was a penny. After removal of the obstruction the esophagus was examined. Marked dilatation of the lower third was observed, and a constriction  $\frac{1}{2}$  cm. in diameter at a distance of 25 cm. from the incisor teeth. The distance for a child of this age should be about 27 to 30 cm. The stricture was dilated and it was then found that a sound, 1.6 cm. in diameter could be passed. The child could then take soft solids without discomfort. Figure 5 shows the stricture after the obstacles had been



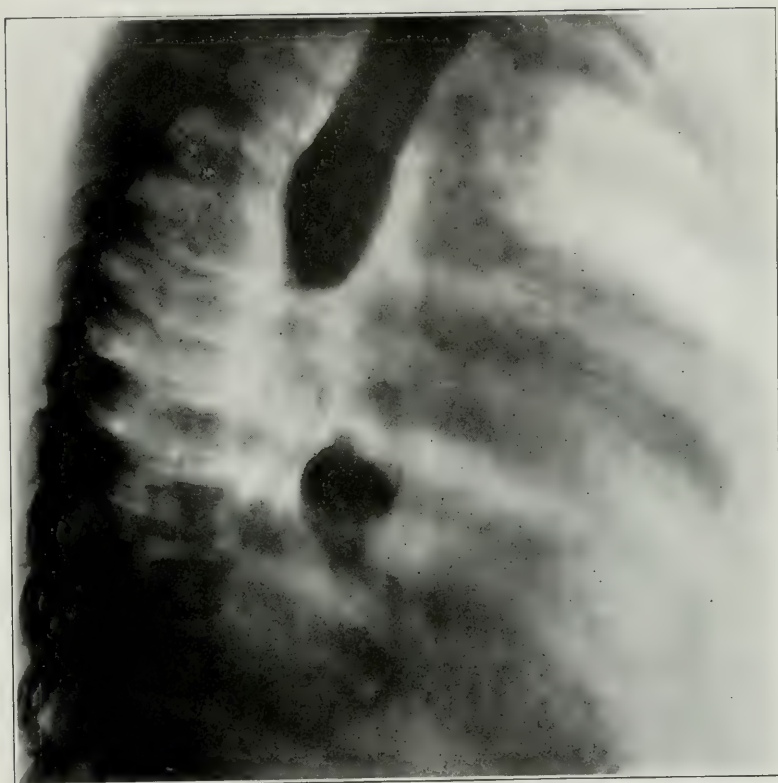


Fig. 1.—Stricture of the esophagus.

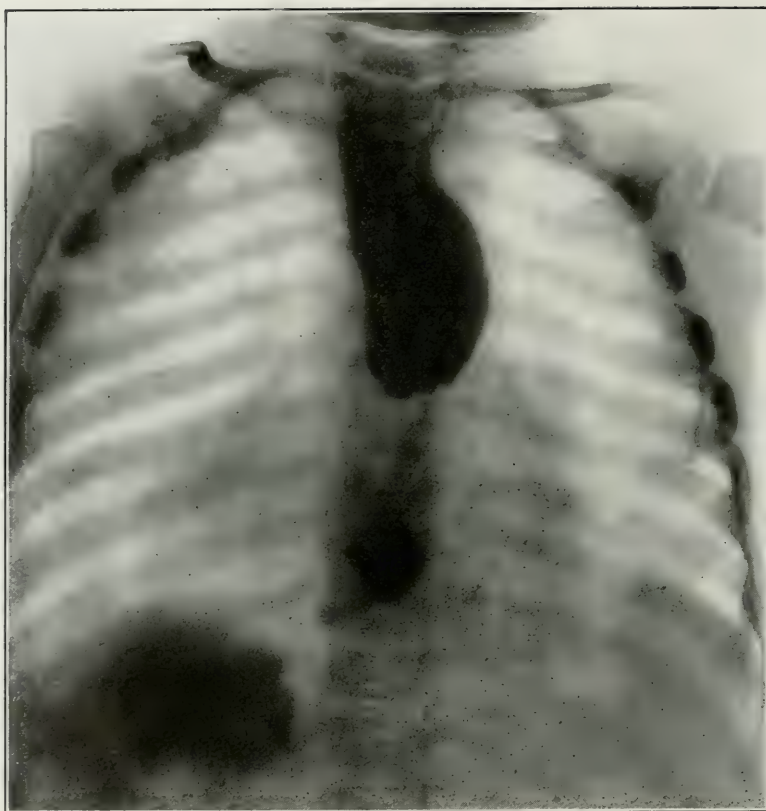


Fig. 2.—Stricture of the esophagus showing that a portion of the bismuth meal had trickled through the stricture into the stomach.





Fig. 3.—Stricture of the esophagus. A portion of the bismuth meal has trickled through into the stomach.

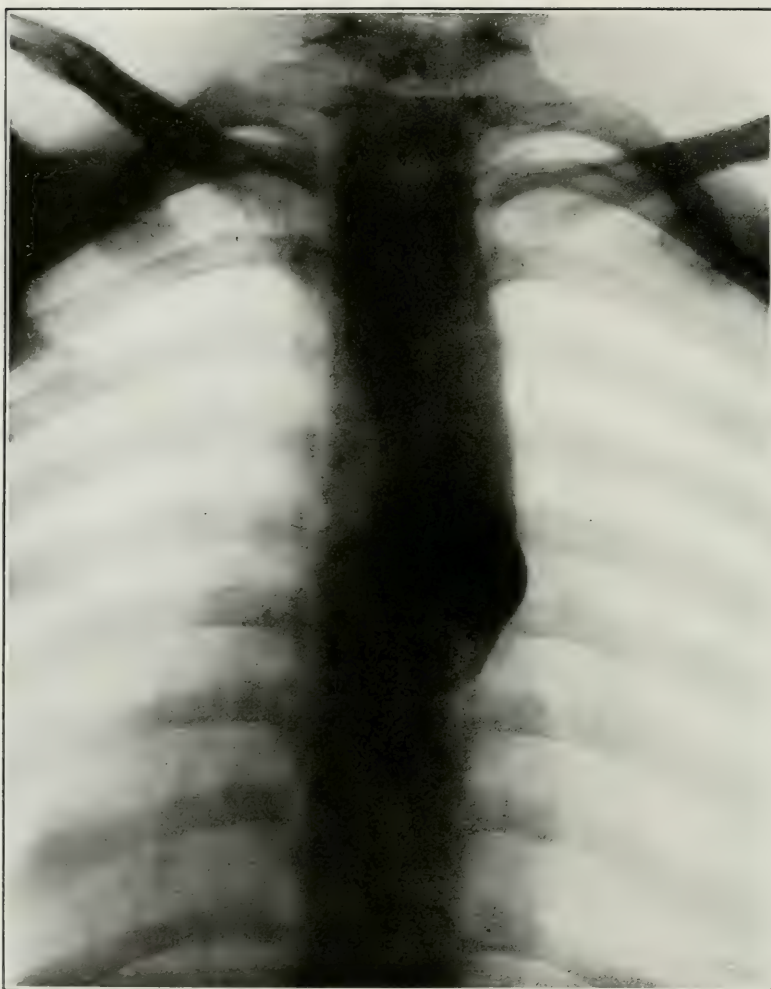


Fig. 4.—Stricture of the esophagus in a girl 10 years old, showing that the bismuth has passed only a little way beyond the middle of the esophagus.

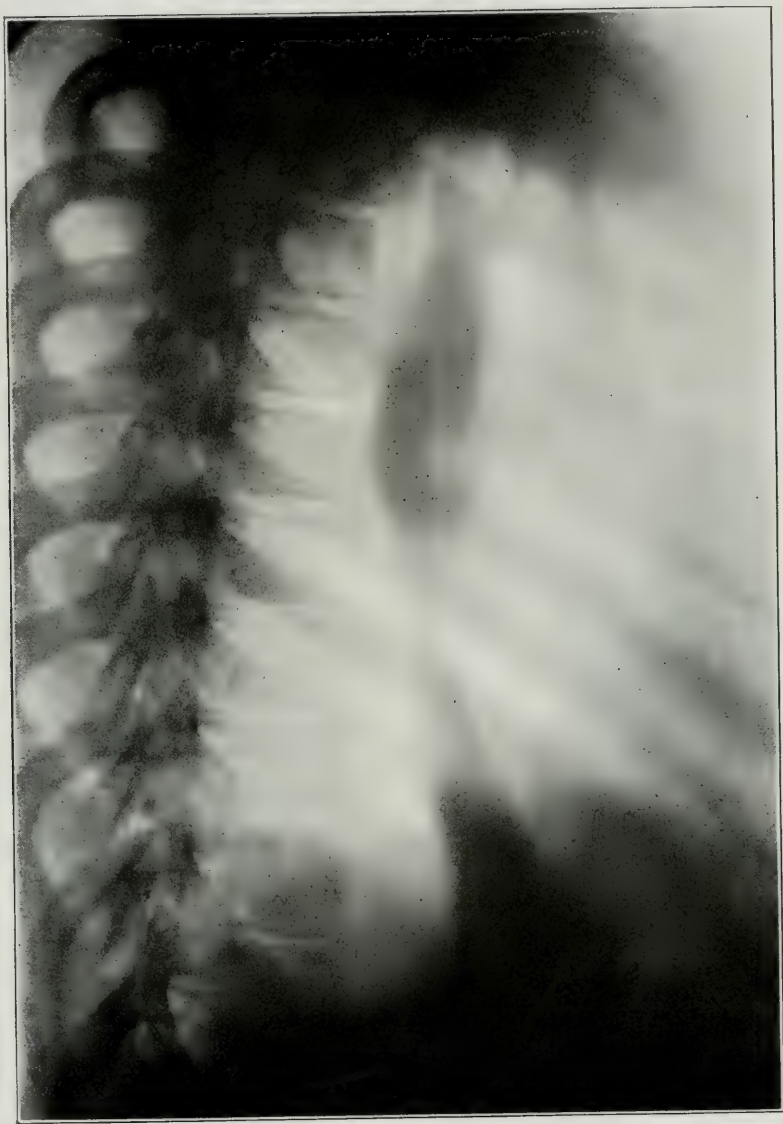


Fig. 5.—Stricture in same case as Figure 4 after obstruction in the form of orange pulp and a penny had been removed and dilatation performed.

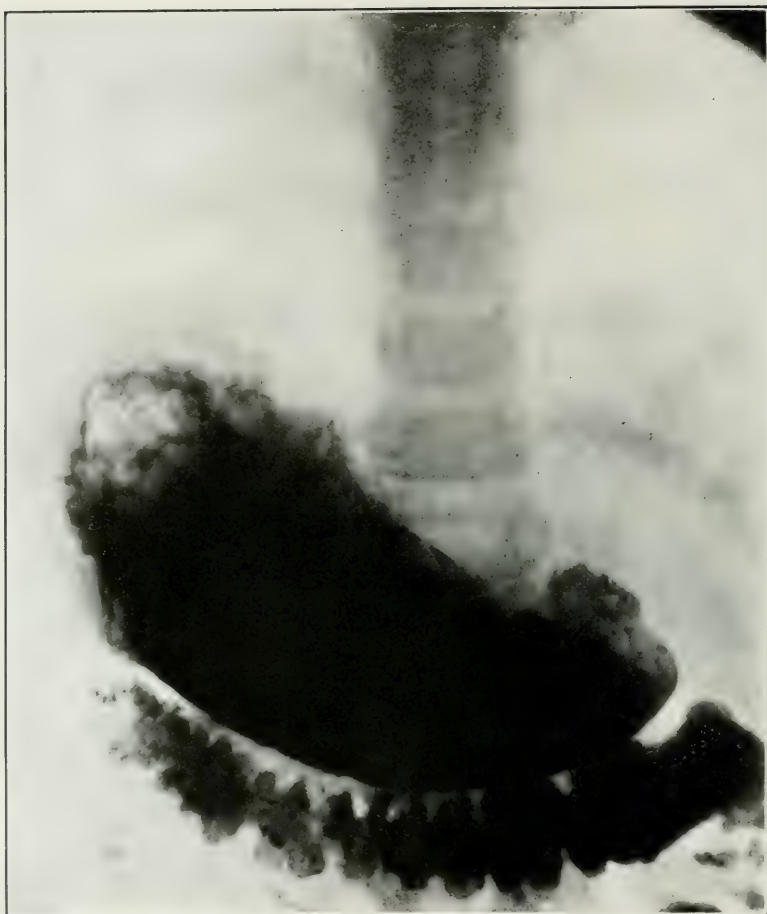


Fig. 6.—Stricture of the esophagus of the spastic variety in a boy  $5\frac{1}{4}$  years old. The bismuth is shown as having passed into the stomach. There was no pyloric stenosis.



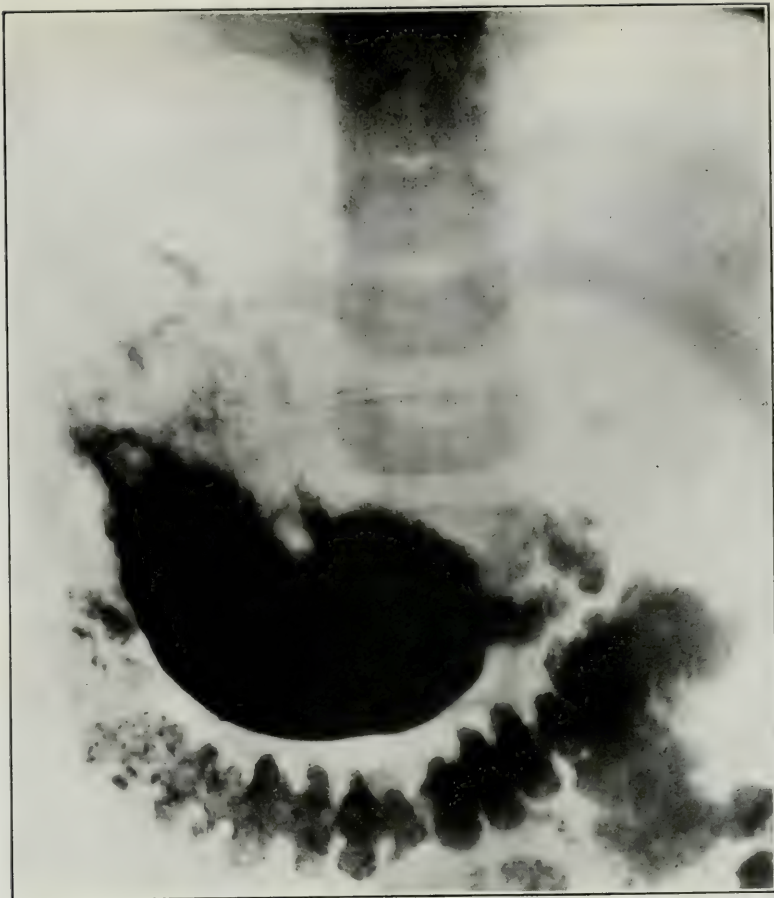


Fig. 7.—See Fig. 6 for description.



Fig. 8.—Showing the stomach tube in the stomach after brief resistance at the cardia. Same case as Figures 6 and 7.

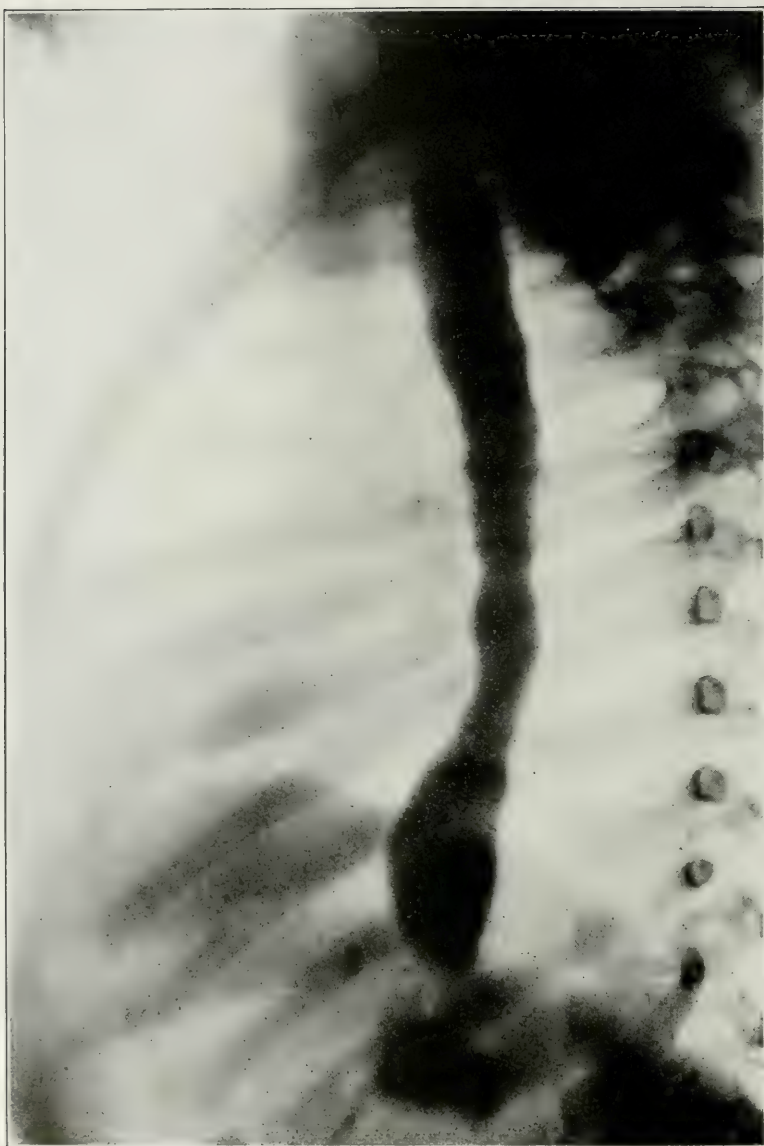


Fig. 9.—Same case as Figures 6, 7 and 8, the child lying on his face, the esophagus full of bismuth and the presence of a stricture in the cardiac end of the stomach.

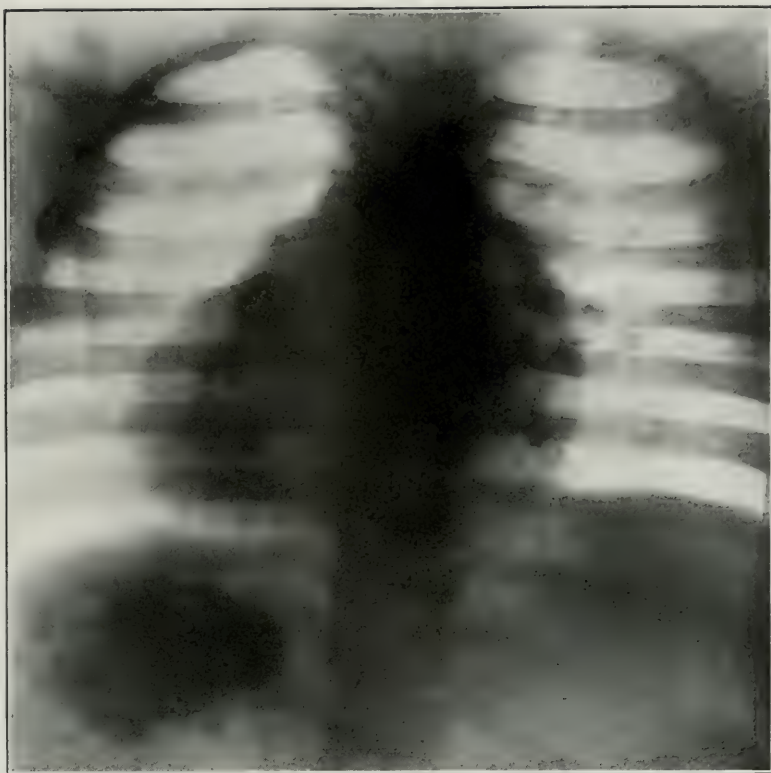


Fig. 10.—Same case. Roentgen picture taken after bismuth meal, following treatment by dilatation, showing that the bismuth has passed freely into the stomach.

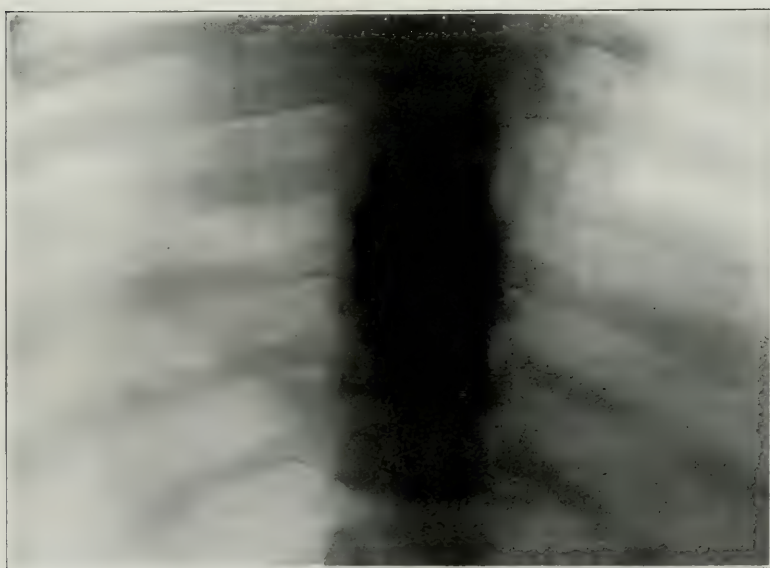


Fig. 11.—Same case. On a recurrence of the symptoms, this radiograph was taken, showing the presence of a coin which was prevented by spasm from entering the stomach. It was removed with the aid of the esophagoscope.

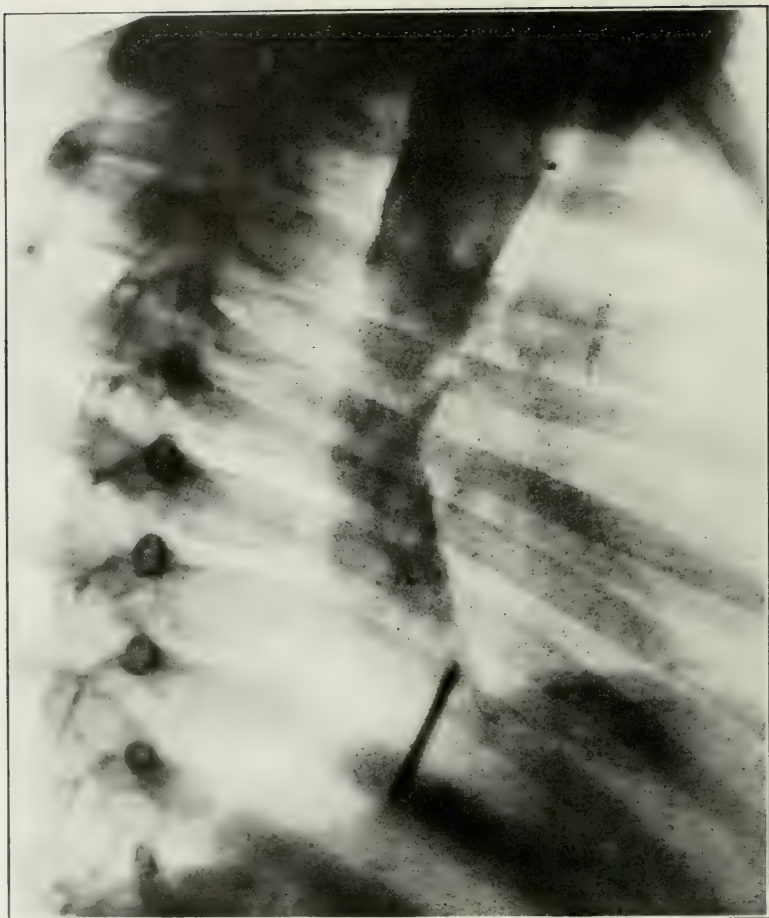


Fig. 12.—Same case. A week later, vomiting having recurred, the esophago-  
scope was passed and a piece of bristle discovered, which was removed. It had  
caused spasm.



removed. The child gained in weight and strength and after having the esophagus dilated at intervals, got entirely well, and on leaving the hospital was eating the regular house diet.

This patient is one who, from time to time, should be treated by dilatation through the esophagoscope, and will, under these conditions, probably continue to do well. The intervals for necessary dilatation will grow longer, and eventually dilatation will, in all probability, be unnecessary.

The history and appearance at the first examination inclined Dr. Greene to the belief that the case was one of organic congenital stricture of the esophagus at the cardia, but the subsequent ease with which the resistance gave way led him to believe that it was probably merely a case of cardiospasm. In the etiology of these cases of spasm of the cardia the congenital element is a likely factor. The spasm occurs at the point of normal constriction and is simply an exaggeration of normal spasm. This case, which represents a narrowing of the esophagus on the border line between a local organic condition and one of central spasmodic origin, is of a type exceedingly favorable for treatment.

CASE 3.—The third case is that of a boy  $5\frac{3}{4}$  years old. He was normally developed at birth. So long as he was fed on liquids and soft solids he did not vomit. There was no history of anything corrosive having been swallowed. When he was  $5\frac{1}{2}$  years old he began to vomit everything that he ate.

Physical examination revealed nothing abnormal. The bowels had been constipated but he had complained of no pain and there were no other symptoms excepting the loss of weight. The urine was normal.

Bismuth meals were given and Roentgen pictures taken at intervals. These revealed nothing abnormal in the chest, and the bismuth had passed into the stomach and intestines, showing that there was no pyloric stenosis. Figures 6 and 7 show this. He was then given bread and milk and again vomited after taking a few mouthfuls. A stomach tube No. 34 French, was passed and met with a resistance at a distance of 24 cm. from the incisor teeth. The normal distance from the incisor teeth to the cardia at this age, according to Morse, is about 27 cm. After a short time the resistance gave way and the tube was passed into the stomach as shown in Figure 8. The tube was then removed, a bismuth meal given, and a Roentgen picture again taken. Figure 9, the child lying on his face, shows the esophagus entirely full of bismuth and the presence of a stricture near the cardiac end of the stomach. He was then treated by having the stricture dilated every four hours. Later a bismuth meal was given without the tube and a Roentgen again taken. This (Fig. 10) shows that the bismuth has passed freely through into the stomach. Some days later he began to take liquids, having the tube passed only once a day for two weeks. After this he was able to take house diet without vomiting.

Dr. Greene at this time passed the esophagoscope and found that the esophagus was unusually roomy above the cardia, especially at its lower third. Spastic closure of the cardia was noted but this was relieved by slight pressure and the esophagoscope was passed through it. There were no signs of bagging of the esophagus nor any pouch, and the spastic closure of the cardia was always easily obliterated by slight pressure.

The child remained perfectly well for two weeks and then began to vomit everything, even water. A Roentgen picture then showed the presence of a foreign body in the esophagus, and Dr. Greene, by means of the esophagoscope, removed

a quarter dollar. Figure 11 shows the quarter prevented by the spasm from entering the stomach. The child then seemed perfectly well and there was no vomiting for a week. He then began to vomit again and when the esophagoscope was passed it revealed a piece of bristle just above the cardia. This was easily removed by forceps. Figure 12 shows the bristle. Since this time the child has occasionally had a slight spasm of the esophagus and dilatation has been done once or twice. The spasm, however, is growing less and probably will soon cease to appear. The child did not seem to be of a nervous temperament and his parents were not neurotic.

There seem to be two classes of esophageal narrowing irrespective of those of traumatic origin. Both classes will probably be found to be of congenital origin. One of them, however, is a localized organic condition in the walls of the esophagus, while the other is a functional, with possibly an additional organic, congenital condition of a brain center, which is represented by a lack of inhibition.

It is possible that pure spasms of the esophagus are mostly congenital and are located in the brain.

197 Commonwealth Avenue.

# THE INFLUENCE OF ACTIVITY ON THE METABOLISM OF THE CHILD

TOGETHER WITH REMARKS ON THE ARTICLE,<sup>1</sup> "SOME FUNDAMENTAL PRINCIPLES IN STUDYING INFANT METABOLISM," BY FRANCIS G. BENEDICT AND FRITZ B. TALBOT

PROF. DR. MED. ARTUR SCHLOSSMANN  
Director Children's Hospital

AND

DR. PHIL. HANS MURSCHHAUSER  
Scientific Assistant in the Laboratory of the Hospital  
DÜSSELDORF

While former authors have bestowed but little attention on the question of how the subjects of their investigations regarding metabolism behaved while under observation — whether they were still or moved — this circumstance of increased or decreased activity is of the most vital interest the moment we include respiratory metabolism in our investigation. The decomposition of N-containing matter is only to a slight degree influenced by activity, especially in the case of infants; but the decomposition of nitrogen-free matter, and with it the elimination of CO<sub>2</sub> rises immediately, as soon as the subject makes any action, moves or cries. Even in the second experiment which Rubner and Heubner<sup>2</sup> carried out on infants in the Pettenkoffer apparatus, these two authors attached very slight value to the performance of the child. They said:

Physical rest and activity on the part of the subjects may be regarded as nearly, if not entirely, alike: considerable performance is, indeed, quite out of the question. In our estimation the normal child was somewhat more active than the weakly, emaciated child. Such differences, however, may be more or less completely compensated for by sleeping time and depth of sleep. In these slight differences of course is included also that which might at the time be termed individual characteristics. Hence with the matter under consideration one will be in a position to judge with all possible acuteness the effects of various forms of nourishment on the child.

We see that here *the significance of the child's accomplishments is still completely undervalued*. Here also a parallel is drawn between the normal child and the emaciated one in computing the transformation, a thoroughly inadmissible comparison, as we know to-day, for it is just the emaciated child that because of the abnormality of its superficies shows an abnormal giving-off of heat. In the first experiment of Rubner

1. Benedict, F. G., and Talbot, F. B.: *JOUR. DIS. CHILD.*, September, 1912.

2. Rubner and Heubner: *The Artificial Nourishment of a Normal and an Emaciated Child*. *Ztschr. f. Biol.*, 1899, xxxviii, 315.



and Heubner<sup>3</sup> these authors go so far as to state that the infant does not accomplish mechanical work to any extent worth mentioning.

But the importance of the child's activity is already recognized later by Rubner and Heubner themselves. In their third experiment they had an unusually sturdy and well-developed boy to deal with, who, by his activity, added extraordinary difficulty to their experiment. This child in the four days of observation put on 1.49 gm. N. According to this, an increase in weight of 70.5 might have been expected, instead of which the weight remained stationary and N-free substance was eliminated. Quite logically, Rubner and Heubner concluded from the figures obtained, above all from the fact that more C was eliminated than absorbed, that it is true albumin was formed, but that on the other hand, N-free substance, that is, fat or glycogen, was exhausted. The child must certainly have behaved itself in an excessively refractory manner while under observation. Heubner<sup>4</sup> says on this point:

On the first day the child began to express in lively fashion his dissatisfaction with the new situation in which he found himself, not only by crying, but by literally raving, exerting all his sturdy muscles most strenuously in order to free himself from his imprisonment. On the next day, when he had accustomed himself to his new surroundings, he certainly cried less, but nevertheless as long as he was awake he was in a state of ceaseless muscular activity, now with his legs, now with his arms. Only during the hours of quiet and usually quite healthy sleep, which took place without interruption at night, were the child's muscles at rest.

Heubner thereupon points out that in this experiment the accomplishment of external muscular work has come to light, and that the consideration of this momentum in the balance of energy, and the possibility of its measurement by a comparison with the formerly observed infants are the most interesting conclusions of this last experiment. He closes his communication with the words that in the future, in judging the effect of nourishment, it will be permissible to take the consideration of the daily performance of crying and rest, and such like, more into account than has been, up to now, frequently the custom. In this publication, then, the significance of outward activity for the energy transformation of the infant is in general and in theory recognized, but the right conclusion as a basis for further investigations is not drawn. This conclusion must run as follows: *In physiological respiration experiments outward activity must either be totally excluded or we must measure the quantum of this activity and consider it in our calculation.*

3. Rubner and Heubner: The Natural Nourishment of an Infant. Ztschr. f. Biol., 1898, xxxvi.

4. Heubner: A Further Contribution to the Knowledge of the Balance of Energy in the Infant. Verhandl. d. Gesellsch. Kinderh., 1904, xxi. Published by I. F. Bergmann, Wiesbaden.



In the observations undertaken by us, we have for years excluded, as far as possible, the outward activity of the subject. But as, indeed, the kind and quantity of the nourishment taken influences the excretion of  $\text{CO}_2$  and the consumption of  $\text{O}$ , we set ourselves to carry out our experiments on sleeping and fasting children. From the outset it seemed difficult to let a child fast for over twenty-four hours, without its subsequently spoiling the experiment by restlessness. But it was found that these things are easier to carry out in practice than they would appear in theory. If, for example, a breast-fed baby is accustomed to take the mother's milk not directly from the breast, but from a bottle, the milk having been drawn from the mother, then it is easy to give this breast-fed baby, now accustomed to the bottle, a bottle filled with water that has been sweetened by saccharin instead of the bottle of milk. It must only be endeavored to suit the saccharin substitute to the child's taste. Let infants but consume the necessary quantity of fluid, and they bear hunger at times splendidly; i. e., they do not notice their hunger at all; they are not conscious of the fact that their life depends on their reserve






	= Awake, crying		= Moving energetically
	= Crying		= Sucking
	= Moving slightly		= Asleep

Fig. 1.—Explanation of signs. (See Fig. 3.)

forces. Of course, the natures of children, just like their temperaments, are different, and for such experiments one must be able to find out the suitably phlegmatic ones. Whoever is to a certain extent acquainted with the psychology of children will seldom miss the mark in the choice of his subjects.

Our procedure is, as a rule, that the child last receives nourishment at 7 o'clock in the evening, then in the morning, and all the next day it has water and saccharin and is petted a great deal. Older infants are played with and as far as possible kept happy, so that they soon go to sleep after having been put in the apparatus; or they are allowed to go to sleep beforehand and the experiment is begun with the sleeping child. Generally, we begin the experiment at 7 o'clock in the evening; the child has then fasted for twenty-four hours, and the effect of nourishment on the organism is eliminated. If one has good luck now and the child sleeps quietly in the apparatus for some hours, the experiment may be considered as an excellent one: *absolute physical rest in a fasting con-*

dition. The value of the excretion of  $\text{CO}_2$  and the consumption of O, which we have ascertained in this manner, give us a glimpse of the *fundamental transformation of the infant. Fundamental transformation is the transformation of a person, reposing and fasting, that finds himself in comfortable, warm surroundings.*

Every movement made by the child increases the transformation of matter, and so increases the excretion of  $\text{CO}_2$  and the consumption of O. For a physiological experiment, repose is the unconditional assumption, and we fully share the view recently expressed by Benedict: "Only periods of complete muscular repose are of any value." In their article in this Journal, also, Benedict and Talbot say very rightly:

While it is not necessary to show that the metabolism of an active crying infant must of a necessity be considerably higher than that of a quiet child, it is not so well known that it is wholly illogical to compare metabolism of an active, restless, normal baby with that of a quiet, sick baby, since the amount of carbon dioxid excreted depends on the degree of muscular activity.

In order now to register whatever movements the children make while under observation, Benedict and Talbot<sup>5</sup> have described an apparatus which mechanically makes a graphic record of the child's movements. We have devoted the greatest attention to these movements in our researches, but have adopted another method of registering them. Thus Benedict and Talbot are not correct in writing:

In all previous determinations of infant metabolism, either of direct energy transformations or by means of the direct calorimetry, either no recognition has been given to the significance of muscular movements on the part of the child, or it has been assumed that the child, when not crying or obviously restless, was quiet and with constant muscular activity. In other words, the notes accompanying these reports said, that the baby was either crying or quiet, i. e., asleep. The difficulties incident to securing long experimental periods of constant muscular activity with infants are only too well known, and yet an examination of the literature shows that almost invariably all of the longer experiments on infant metabolism have included periods of obviously great muscular restlessness and activity, as well as periods of crying.

We, on the contrary, have in all our researches in later years observed the child, and recorded the behavior of the child from quarter minute to quarter minute by quite definite signs. In Figure 1 is given the explanation of the signs employed by us. Figure 2 shows an ideal experiment, in which during three hours our child only twice made quite a slight movement in its sleep; and Figure 3, on the other hand, shows an experiment in which the child was decidedly restless. As has been said, all the experiments that we have published in the last few years show clearly how the child has behaved from minute to minute. Indeed, we adhere to the point of view that it is of absolutely no value to carry out and publish respiration researches in which this fundamental requirement is not complied with.

5. Benedict: Deutsch. Arch. f. klin. Med., 1912, cvii, 192.

It may appear questionable which is the better: the graphic method which we employ, which depends on individual observation of the child and on notes made two to four times per minute, or the mechanical record of Benedict and Talbot. Against our method it may with reason be objected that the judgment is exposed to the unavoidable vacillations of the observer. One and the same movement will be at one time recorded as being of a greater degree and at another time as being of a lesser degree, or *vice versa*. On the other hand, it is certainly to be remarked that the principal participators in our researches, since we have been working in Düsseldorf, are always the same persons, and not only the two authors of this article, but also the analyst of the laboratory and the

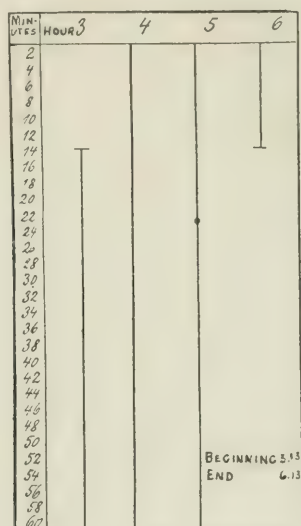


Fig. 2.—An ideal experiment, in which during three hours the infant (L) only twice made a slight movement in its sleep.

attendant. Hence a certain uniformity in the observance of the children's condition is assured and a possibility obtained of comparing the various experiments with each other.

But the method of Benedict and Talbot has also its disadvantages. The crying of the children, for instance, indicates a very considerable degree of activity, which is mainly performed by the respiratory muscles. But this activity will make slighter marks on the tambour than a movement of the leg or arm, in which less mechanical work is performed. Sucking movements of the child's lips will be not at all, or scarcely at all, visible, because a movement of the support under the child will not be affected by such an action, confined as it is to a single group of muscles. In short, a mechanical record, also, with all the aids to be had



therewith, will just as little render possible an absolutely exact view of the accomplishment, as the recording of personally observed movements. But under all circumstances — whichever method is used — exact observation of the activity in experiments with the respiration apparatus must be ensured, and included in the publication of these researches, if the observation is to have real value. On this point there is between Benedict and Talbot, on the one hand, and ourselves on the other hand, a perfect conformity of view.

Perhaps we may be allowed to take this opportunity of informing our American colleagues that it was possible for us to ascertain the worth of the fundamental transformation of the infant, which may be of value for further researches as standard figures. We found<sup>6</sup> that an infant of 4,325 gm., fasting and in complete repose, exhausted

9.03 gm. albumin  
12.88 gm. fat and  
23.32 gm. glycogen

of its physical reserves; that is, 273 calories. Fundamental transformation is accomplished in the cases of various infants, *ceteris paribus*, in proportion to the superficies; 1 sq. m. infant superficies has thus a fundamental transformation of 859 calories. By this means we can deduce the fundamental transformation of any normal infant with whose superficies we are acquainted, or whose superficies we can compute from its weight. The fundamental transformation of the infant fully synchronizes, moreover, with that of the adult, if here also the bodily superficies is reckoned as the basis of comparison; for Atwater found in adults a fundamental transformation of 840 calories per square meter, a figure which coincides ideally with that ascertained by us.

Now that we know the fundamental transformation, we can obtain a genuine conception of the accomplishment of the infant. One child whom we had under observation<sup>7</sup> cried during a part of the experiment, and at the same time made lively movements. In so doing, it exhausted per hour 2.764 liters more O than during the time of rest, that gave us a result *re* the fundamental transformation. From the increased consumption of oxygen, and from the increased formation of CO<sub>2</sub> it may be deduced that the child in this hour of unrest transformed 13.27 calories more. That is, then, 13.27 times 425 = 5,640 kg. of chemical

6. Schlossman and Murschhauser: The Fundamental Transformation and Nourishment Requirement of the Infant According to Researches on Gaseous Exchange. *Biochem. Ztschr.*, 1910, xxvi.

7. As regards the behavior of this child while under observation, our report says: "It behaved itself in a very refractory manner, moved energetically, cried so that it grew red, and was not to be pacified." This description is strikingly similar to that which Heubner gives of the restless infant that he and Rubner had under observation.



energy, which were used in the activity of crying and during activity. Even if only the third or fourth part of these 5,640 kg. is to be accounted as really mechanical work, then this child of  $51\frac{1}{2}$  kg. accomplished work to the extent of from 1,400 to 1,900 kg. In another case we were able to ascertain that a fretful child of 2,680 gm. exhausted 0.785 liters more O per hour by crying. That, with a respiratory quotient of 0.90, corresponds to 3,899 calories, or 1,657 kg. of chemical energy transformed. Thus that would signify an actual attainment of about 500 kg., which this child of 2.68 kg. achieved by crying.<sup>8</sup>

If we, judging from our knowledge of the infant's fundamental transformation, consider the two breast-fed babies that served Rubner

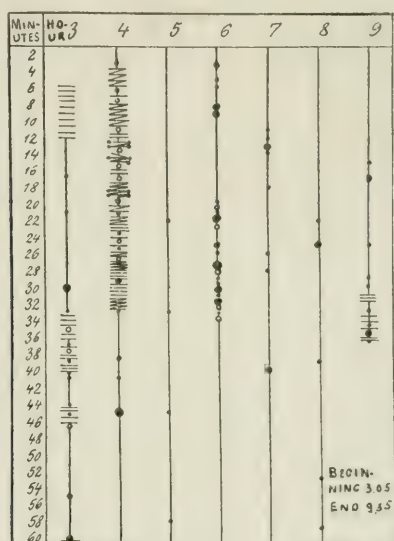


Fig. 3.—Experiment in which the child (P) was extremely restless. See Figure 1 for explanation of signs.

and Heubner in their experiments, in which the respiratory exchange, at least with regard to the excretion of carbonic acid, was ascertained, the following is shown: The first breast-baby, with a weight of 5,250 gm. and a superficies of 0.3500 square meters, absorbed 379.95 calories and decomposed 351.78 calories per day. The requirement for the fundamental transformation for this child amounted, according to our researches, to 300.65 calories. Thus there were used for activity expended 51.13 calories, and the fundamental transformation was exceeded by the accomplishment by 17 per cent. That corresponds to a chemical energy of 21.730 kg., or an attainment of over 5,000 kg. per day, if we assume an

8. Schlossmann and Murschhauser: On the Influence of Crying upon the Respiratory Metabolism of the Infant. *Biochem. Ztschr.*, vol. xxxvii.

exhaustion of chemical energy of 25 per cent. for activity and 75 per cent. for formation of heat. The child elevated its weight about 1,000 meters in twenty-four hours, if we think of the manifold movements simply as a work of elevation. As the child at the same time slept a great deal, it accomplished during its waking hours extremely important mechanical work, contrary to the opinion of Rubner and Heubner that the infant does not perform mechanical work to an appreciable extent. The second breast-baby that Rubner and Heubner observed<sup>9</sup> was a perfect little acrobat. He weighed 9.77 kg., his superficies amounted to 0.5464 square meters, and he decomposed 660.5 calories. According to our researches, the fundamental transformation of this child amounts to 469.4 calories; consequently, the child transformed 191.1 calories more than were necessary for maintenance. But a total energy of 81,217.5 kg. is transformed from a potential state to a kinetic one, thus an effective work of around 20,000 kg. So the child elevated his own weight in twenty-four hours about 2,000 meters. The increase of the force transformation compared to the fundamental transformation amounted to 47.1 per cent. If one assumes that the child was absolutely quiet for twelve hours, it transformed in the twelve hours of activity about 100 per cent. more than when at rest; and so accomplished exactly as much as a child under our observation that cried for an hour and made energetic movements.

The description which so eminent an observer as Heubner gives of his subject, characterizes it as an excellent accomplishment. He says: "The child cries almost incessantly, has a reddened face, great beads of perspiration on face and arms," etc., all an indication of unusually strong, physical exertion, for which our figures give us abundant proof.

From all that has been said here it is proved of what great importance is the observation of children with regard to their movements and behavior during the carrying out of metabolism researches. Therefore, there was forced on us the importance of proving that we have ascertained by exact research the actual transformation during repose, and that for years in all our researches we have made exact records of the manner and intensity of movements on the part of our subjects.

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9. *Ztschr. f. Biol.*, 1898, xxxvi; *Ztschr. f. exper. Pathol. u. Therap.*, vol. i.

## IS DIPHTHERIA FREQUENTLY A BACTEREMIA? \*

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In August last, Conradi and Bierast<sup>1</sup> of the Hygienic Institute of the University of Halle reported the results of an extensive examination of the urine of diphtheria patients. They call attention to the fact, that, while diphtheria has been regarded as essentially a local disease, yet the Loeffler bacillus has frequently been isolated from the blood and organs after death, and occasionally from the blood during life, usually, however, in the agonal stage of the disease. On account of the technical and other difficulties of obtaining a sufficiently large quantity of blood from diphtheria patients, they sought to solve the question of diphtheria bacteremia by an indirect method, namely, an examination of the urine of those actively ill, and of convalescents. In all, 155 patients were examined, of whom fifty-four showed a positive urine. In six cases only, however, were virulence tests made, all of which proved positive. As the material was sent to the research laboratory at random, there was no possibility of following up a given case in order to study the question of the persistence of the bacilli by repeated examination. Of the 54 positive cases, 32 were female and 22 male; 36 children, 18 adults. Thirty-one urines were taken in the first week of illness, 10 in the second, 5 in the third, and 2 in the fourth. One was found positive in the ninth week of convalescence. The urine, 20 to 30 c.c. in amount, was taken by means of a sterile catheter with every precaution against contamination, and the centrifugalized sediment spread over one or two Loeffler plates and plates of Conradi and Troch. Both Loeffler and Neisser's stain were used for identification. The bacteria were found in normal as well as albuminous urine, showing that they pass through healthy as well as diseased kidneys. In most cases they were very few in number.

No clinical data are furnished in regard to the severity or outcome of the cases giving positive results. On the strength of their findings the authors make a plea for the disinfection of the urine of convalescents, until, by three negative cultures, it is shown to be free from diphtheria bacilli. They suggest that diphtheria of the skin and mucous membrane, which shows such a predilection for the genital and anal regions, is due to direct infection from the urine, and that the mystery that surrounds

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\*From the Research Laboratory, Department of Health, New York City.

\*Read at the meeting of the American Pediatric Society, Washington, D. C., May, 1913.

1. Conradi, H. and Bierast: *Deutsch. med. Wchnschr.*, Aug. 22, 1912, No. 34.



the origin of certain local epidemics of diphtheria may be explained in the same way.

Dr. R. Koch<sup>2</sup> of Frankfort, in December, reports the results of his examination of 111 urines from 26 patients. In 4 of these, which came from two patients, virulent diphtheria bacilli were found. In 10 urines from 5 other patients, diphtheria-like bacilli were found, which either could not be isolated in pure culture or else proved to be avirulent. In the original smears diphtheria bacilli were never recognized.

The urine was passed into a sterile vessel after thorough cleansing of the meatus with mercuric chlorid solution. In 74 examinations made on 19 patients suffering from mild or moderately severe diphtheria—in one case 14 examinations were made in 25 days—no suspicious organisms were found. In 5 other patients diphtheria-like organisms were found which proved to be avirulent; 2 of these were fatal cases. Post mortem examination of the urine proved negative.

Of the two positive cases, both ended fatally from the toxemia of the disease and cardiac paralysis. The first showed negative urine on the first two examinations, virulent diphtheria bacilli being found on the seventh day, the patient dying on the following day. In the second case they were found on the fifth day of the disease and the following day, being absent on the next five days and present on the twelfth day again, the patient dying the next day. The appearance of the bacilli in the urine was in neither case coincident with change in the general symptoms. The presence or absence of albumin in the urine had no bearing on the presence of bacilli.

Nineteen cases of scarlet fever complicated by diphtheria were examined as controls. In four of them the urine contained diphtheria-like bacilli which proved to be avirulent. We believe that only animal tests can be relied on for the identification of diphtheria-like bacilli in the urine. While Loeffler bacilli may occasionally occur in very severe cases, the fact is not of practical interest, as such patients, being confined strictly to bed, would not be likely to be a source of danger through infected urine.

The latest writer on the subject is Walter Beyer<sup>3</sup> of Rostock, whose reported results are little short of startling. He examined nineteen cases of diphtheria daily, or every second day, from the active stage of the disease to late convalescence. Forty c.c. or more urine were taken with proper precaution against contamination, and the centrifugalized sediment poured over a Loeffler plate. Practically every urine examined showed diphtheria bacilli at each examination; their number being greatest during the active stage of the disease and gradually diminishing.

2. Koch, R.: *Deutsch. med. Wehnschr.*, Dec. 12, 1912, No. 50.

3. Beyer, Walter: *München. med. Wehnschr.*, Feb. 4, 1913, No. 5.



In the case of eight convalescents, four of whom had recovered from their illness, three and one-quarter to three and one-half months previously, and the others eight, six, five and four weeks, respectively, the urine showed the continued presence of diphtheria bacilli, six strains of which were said to have been virulent for guinea-pigs, the other two avirulent. In all of the eight cases cultures from the tonsillar crypts showed diphtheria bacilli. It is to be noted that there is nothing said by Beyer or Conradi as to their methods of testing for virulence; that is, as to whether antitoxin was used in the test.

Beyer believes that it has been established beyond doubt that in the early stages of diphtheria, at least, the disease is essentially a bacteremia. Whether the organisms found in convalescents constitute also an evidence of a continued blood-infection he does not undertake to say.

Our series of cases comprises 54 patients with 56 examinations of urine. These were divided into three groups roughly corresponding to the type of disease which characterize the clinical material from which the three observers quoted obtained positive results. Thus the first group, 25 in number, consisted of routine cases; the second, 21 in number, cases of the severer type with a great deal of membrane and showing symptoms of toxemia; third, 8 in number, cases of recent convalescents. All were patients at the Willard Parker Hospital.

In the first group, there were 5 adults and 21 children, the ages of the latter ranging from 2 to 13 years. There were 18 males and 7 females. Twelve patients were in the first week of the disease, 7 in the second, 3 in the third, 1 in the sixth week and 2 not determined. Only 1 or 2 of these cases were of any severity. The urine proved negative in every case.

In the second group of 21 cases there were 4 adults and 17 children, the latter 2 to 11 years, 16 males and 5 females. Twenty were ill for a week or less at the time of taking the urine and 1 with croup and cervical adenitis for sixteen days. Two of this group proved positive. One, Edward M., 8 years of age, two days ill, had thick membrane covering the tonsils, fauces, uvula and posterior walls of the pharynx; there was also nasal discharge and marked toxemia. The serum tube and ascitic broth showed Loeffler bacilli which proved to be virulent. A specimen taken one week later was negative. The patient made an uneventful recovery. A second patient, Sam G., aged 5 years, had been ill three days. The patient had thick membrane on both tonsils, uvula and pharynx with profuse purulent nasal discharge. The cervical nodes were swollen and the patient very toxic. The serum tube and broth showed virulent Loeffler bacilli. The second specimen, taken eight days later, proved negative. Neither of these patients were catheterized on either occasion. Of the remainder of this group, from one, Hoffman's bacillus

was isolated, and from a case of diphtheria complicating scarlet fever and sepsis a specimen taken by catheter showed diphtheria-like bacilli, which, however, proved not to be diphtheria. All the other cases were negative.

#### TECHNIC

In the first two groups the female patients were catheterized, 20 or more c.c. of urine being drawn into a sterile centrifuge tube. In the case of males the first part of the urine was discarded and the residue passed into sterile centrifuge tubes through a sterile glass funnel. In one or two instances very young males were catheterized. In three cases only 8 to 12 c.c. of urine was obtained. The centrifugalized sediment was treated as follows:

One c.c. was drawn off by pipet, 0.8 of which was put into 3 to 4 c.c. of ascitic broth and the remaining 0.2 poured over a Loeffler serum tube and incubated. Colonies developing on the tube were examined in the routine way, and if any pellicle developed on the broth, it was stained with Loeffler's methylene blue and examined.

In the third group, although we had every confidence in our technic in producing equally if not more definite results than theirs, it was thought advisable to follow exactly that of the three writers quoted. The patients were catheterized after thorough cleansing of the meatus with mercuric chlorid solution and 35 to 40 c.c. of urine drawn into a sterile container. The centrifugalized sediment with 1 c.c. of the urine was drawn off by pipet and one-half of the quantity allowed to flow over each of two Loeffler plates previously tested with a known strain of Loeffler bacillus. In addition, in four cases 5 c.c. of the remaining urine was put into 75 c.c. of ascitic broth.

In this group there were eight patients, five of whom were females, five children and three adults. With one exception, they were all cases of clinical diphtheria of a pronounced type; the exception was a case which showed only a markedly congested pharynx from which cultures taken on several different days showed typical diphtheria bacilli. The patients had been ill from three to twelve days and were mostly afebrile at the time of the test. All showed the presence of diphtheria bacilli on culture in the throat.

In three cases there was no growth on the plates after twenty-four hours; in the other five, only colonies of cocci were present, probably staphylococci. The ascitic broth also proved negative.

#### CONCLUSIONS

The two positive findings in our series may well have been due to accidental contamination at the time of taking the urine, especially as a catheter was not made use of in either case. We conclude, therefore, that diphtheria bacilli may occasionally gain access to the blood and be

excreted in the urine in very severe cases of diphtheria with marked ulceration of the mucous membrane of the pharynx and tonsils. This fact is of theoretic interest, but of little practical importance to the physician. Finally, we believe that identification of diphtheria bacilli in the urine should not rest on morphologic characteristics alone, but be confirmed by isolation and animal inoculation controlled by the use of diphtheria antitoxin.

# SIMPLE SYRINGE TRANSFUSION WITH SPECIAL CANNULAS

A NEW METHOD APPLICABLE TO INFANTS AND ADULTS  
PRELIMINARY REPORT \*

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The entire apparatus for simple syringe transfusion consists of two sets of cannulas, two tourniquets and twelve syringes.

## CANNULAS

Two sets of cannulas are employed, one for the donor, the other for the recipient (Figs. I and II).

There are three cannulas to each set (Fig. II; 1, 2, 3). Each cannula telescopes within the other as shown in Figure I.

The innermost cannula is practically a hollow needle, 2 6/16 inches long, 20-gage, with one end ground to a fine point and short bevel. The hollow needle (1, Fig. II) is fitted snugly into Cannula 2. Cannula 2 is 5 mm. shorter than the needle and is fitted snugly into Cannula 3. Cannula 3 is 5 mm. shorter than Cannula 2. The proximal ends of 1 and 2 are capped with stationary thumb-screw caps.

The proximal end of 3 is capped with a receiver to fit any Record syringe.

Cannula 3 is 2 inches long, 14-gage, .064 diameter. The caliber of this cannula is the same as the tip of a Record syringe.

In very small infants with very small veins only Cannulas 1 and 2 are employed, 2 being capped with the receiver to fit tip of syringe.

The syringes used are Record syringes of new improved type with a capacity of 20 c.c. and can be sterilized by boiling.

## OPERATION

One operator manages syringe of recipient. Another operator manages syringe of donor. An assistant stands between operators, who are in a position close to the assistant. Donor and recipient are placed in the recumbent posture. Suitable veins are selected.

In adults and most children over 2 years of age the median basilic is easily accessible. In infants the external jugular or one of its tributaries is entered more advantageously. In some cases the internal saphenous may prove the vein of preference.

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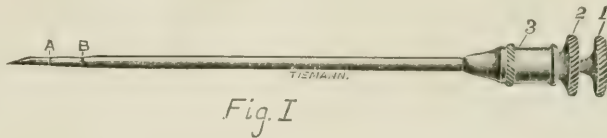
\* Read before the Pediatric Section of the New York Academy of Medicine, April 10, 1913.

\* Manuscript submitted for publication April 19, 1913.

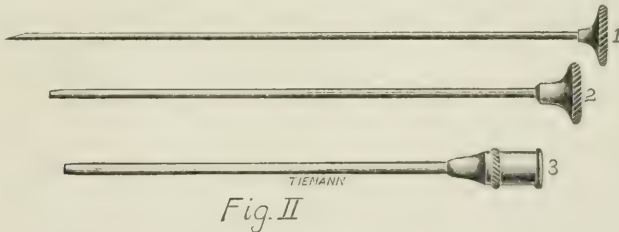


A tourniquet is placed in position, and the skin is sterilized with iodin. The cannula is then held in a position almost parallel to the vein with the thumb on the thumb-screw cap of the innermost cannula (1, Fig. I). The skin is then punctured and the cannula is forced into the vein. After the first joint A has entered vein, Cannula 1 is withdrawn a distance of about one-half inch. (This prevents the vessel wall from being injured or punctured by the needle after the vein is entered.)

With the thumb now on the thumb-screw cap of 2 the cannula is forced further in until the second joint B (Fig. I) has entered the vein. Cannula 2 is then withdrawn a distance of about one-half inch.. (Cannula 3 alone can come into contact with the vessel wall.) Cannula 3 is then gently pushed into the vein to a desirable length; usually three-quarters to one inch will suffice.



Cannulas 1 and 2 are now withdrawn entirely. If the vein has been successfully entered, blood will flow through the cannula. When the first drop appears a syringe containing warm saline solution is immediately attached and a very slow flow of saline is maintained through cannula. Escape of blood is thus prevented.



There is no need of haste at this stage.

A cannula is next inserted in vein of donor in a like manner; again a syringe containing warm saline is attached and loss of blood thus prevented. Everything is now in readiness for the transfusion. An empty syringe is substituted for the one containing saline solution, and blood is withdrawn from donor as rapidly as possible. When the syringe is full the assistant passes it to the operator on the recipient, who removes its saline syringe, attaches the syringe containing blood and evacuates the contents gently but speedily into the vein.

One syringeful of blood is followed by another in rapid succession until the desired quantity of blood has been transfused.

A little normal saline is injected through cannula of recipient after each syringeful of blood. This keeps cannula free of blood and precludes the possibility of clotting.

It has been found advisable for the assistant (or third man) to remove the syringe from the cannula of the donor as soon as filled. The operator can thus hold the cannula in place with one hand while with the other hand he may at once adjust an empty syringe into the cannula. Loss of blood is thus reduced to a minimum.

#### CASES

CASE 1.—(January 3, 1913) M. O., aged 9 years, weight 34 pounds. Cannula inserted in right external jugular vein on second puncture. Patient received 20 c.c. blood from a volunteer, blood being taken from median basilic.

CASE 2.—L. P., aged 4½ months, weight 6 pounds 5 ounces. Case of marked malnutrition. Cannula inserted in external jugular of patient on second puncture. Donor, mother. Cannula inserted into median basilic vein on first puncture. Patient received 75 c.c. of blood. Death two days later of malnutrition. No evidence of embolism clinically. Permission for autopsy was not granted.

CASE 3.—(March 19, 1913). J. T., aged 23 months, weight 19 pounds 12 ounces. Cannula inserted in median basilic vein of patient on third puncture. Donor, mother. A large needle instead of cannula was used in this case. This offered considerable difficulty and only 60 c.c. could be withdrawn from median basilic vein. Child received 60 c.c. of mother's blood. No evidence of embolism. Child doing well.

CASE 4.—(March 21, 1913) G. P., aged 6 months, weight 8 pounds. Cannula inserted in external jugular of patient on first puncture. Donor, mother. Cannula inserted in median basilic vein on first puncture. Patient received 90 c.c. mother's blood. No evidence of embolism.

CASE 5.—(March 22, 1913) P. R., aged 11 months, weight 12 pounds 4 ounces. Insertion of cannula in right and left jugular and both median basilic veins of patient failed. Right internal saphenous near ankle was then entered successfully. Donor, mother. Cannula inserted in median basilic vein on first puncture. Patient received 130 c.c. of mother's blood. No evidence of embolism. Child doing well. Hemoglobin before transfusion 50 per cent. Dare; four hours after transfusion, 75 per cent. Dare.

CASE 6.—(March 26, 1913) J. H., aged 4½ years, weight 28½ pounds. Cannula inserted in median basilic vein of patient on second puncture. Donor, father. Cannula inserted in median basilic vein on second puncture. Patient received 160 c.c. of father's blood. Hemoglobin before transfusion 62 per cent. Dare; Hemoglobin March 30, 70 per cent. Dare. Child is doing well and discharged from hospital March 30, 1913. No evidence of embolism.

CASE 7.—(March 26, 1913) N. L., aged 9 weeks, weight 6 pounds 6½ ounces. Cannula inserted into external jugular of patient on second puncture. Donor, volunteer. Cannula inserted in median basilic vein on first puncture. Patient received 50 c.c. of blood. No evidence of embolism. Length of time required in this case was nine minutes from beginning to end of operation.

CASE 8.—(March 29, 1913) M. O., aged 9 years, weight 35¼ pounds. This case is the same child mentioned in Case 1. Cannula was inserted in the same vein used January 3. Single puncture successful. Donor, volunteer, aged 24. Wassermann negative. Hemolytic tests negative. Cannula inserted in median basilic on first puncture. Patient received 280 c.c. of donor's blood. Hemoglobin before transfusion, 45 per cent., hemoglobin 4 hours after transfusion, 75 per cent., hemoglobin April 1, 70 per cent. No evidence of embolism. Child is doing well. Time required twelve minutes from beginning to end of operation.

CASE 9.—(March 31, 1913) G. N., aged 11 months. Cannula inserted in right jugular of patient on first puncture. Donor, mother. Cannula inserted in median basilic vein on second puncture. Child received 110 c.c. of blood. Hemoglobin before transfusion, 55 per cent. R.B.C. 2,800,000. Hemoglobin twenty-four hours after transfusion, 80 per cent. R.B.C. 4,400,000. No evidence of embolism. Time required not more than fourteen minutes. On admission the child had discharging ears and weeping eczema behind the ears. April 3d: Erysipelas about lobe of left ear and parotid region and over nose. Erysipelas present in two other children in ward at the same time.

## RULES

1. Bright polished surfaces of syringe and cannulas are requisite.
2. A syringe used once should not again be employed until thoroughly cleansed with sterile water.
3. Air must be avoided. This, however, offers no difficulty.
4. Tourniquet of patient must be removed after vein is entered with cannula.
5. Tourniquet remains on donor throughout operation; momentary release of tourniquet may be advisable once or twice during course.
6. Dexterity and speed are requisite for success.
7. Syringes can be evacuated more rapidly than they can be filled without any harmful effects. This difference in time allows for attachment of syringe with warm saline following each syringe-ful of blood.

## COMMENTS

The time elapsing in filling and evacuating the syringe is so brief that blood does not undergo any alteration from donor to recipient.

No lubricant has been employed except in one case. Cannulas are lined with a film coating of albolene.

Both arms of the donor may be used simultaneously.

Larger syringes with larger calibered cannulas may be used, but the present sizes have worked satisfactorily and fittings of syringe and cannulas are of universal gauge.

Syringes and cannulas may be kept sterile in individual metal containers. They are thus in readiness for immediate use and no preparation for operation is required.

The same vein can be used repeatedly for subsequent transfusions, since no thrombosis nor permanent injury to vessel occurs, as in Cases 1 and 9.

Any quantity of blood can be transfused and the quantity is definitely measured at the time of transfusion.

No skin incision was made in any of the cases presented in this paper.

Rubber tubings, various pumps and gravity have been employed on animals, but the best results have been obtained with the syringe cannula method.

In a later paper, Dr. LaFétra and I will present some new fields of application of blood transfusion. The present cases with others will be then discussed in greater detail. The object of this paper is simply to present a new and simple method of blood transfusion.

This work was done on the service of Dr. LaFétra in the Pediatric Section of the First Medical Service of Bellevue Hospital. I desire to thank him for the privilege of publishing these cases. I desire also to thank Drs. Stetson, Schroeder and Hill of the house staff, who assisted me in the work.

Since this article was sent for publication, I have done twenty-seven transfusions. These with the nine cases presented above make a total of thirty-six transfusions done by this method. Not a single mishap or untoward complication has occurred. The youngest patient was 7 weeks old, weighing 6 pounds 6 ounces. The largest quantity transfused was in an adult who received 1,200 c.c. The time required from beginning to end of the operation in these cases ranges from three to twenty-three minutes. The length of time the blood remains in a single syringe is from six to ten seconds. No skin incision was made and no anesthetic was given in any case.



## A FORMULA FOR THE DETERMINATION OF THE SURFACE AREA OF INFANTS

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Certain physiological functions are directly dependent on the surface area of the body. The heat elimination, as first shown by Rubner, and the excretion of carbon dioxid and the consumption of oxygen are *pari passu* proportional to the extent of the body surface. The study of the heat production of infants by Rubner and Heubner and Niemann, and of the infants' respiratory exchange by Schlossman, allows one to compare the different infants under the varying conditions of experimentation. They have been studied while fasting and while taking diets of different compositions. Some of the children have been well, some moderately and some poorly nourished. Great care has been used and much labor has been expended in making the different forms of apparatus and the experiments accurate in all details. The metabolism of the children has been compared on the basis of their surface area. It is evident, therefore, that the determination of the surface area should be very exact, for it obviously would be useless to determine the heat elimination painstakingly and with an error of only 1 or 2 per cent., and then use a formula for the surface area which may give an error of 15 per cent. or more. And yet, as will be seen later, this has been the case.

For the determination of the surface area various formulas have been proposed. Meeh<sup>1</sup> was the first to construct a formula for this purpose. He was anxious to obtain one applicable for all ages. His observations include the measurements of only three infants and these were all well nourished. The basis for Meeh's formula was the determination by Molischott that the volume of bodies of similar composition and form varies in the ratio of the cube root of their weight, and their surface areas in the ratio of the square root of their volume. He saw that the difference between the figures obtained from a formula, surface area =  $\sqrt[3]{\text{Weight (in grams)}}^2$  and those from actual measurement would allow him to fix on a constant with which his results could be multiplied and thus surface areas calculated with reasonable accuracy. This constant was 12.3. But while the results for adults with the formula are satisfactory, they are not so for infants, as Meeh himself recognized would probably be the case; and he suggested that a smaller constant should be employed for infants. For this reason Rubner and Heubner used 11.9

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1. Meeh: Ztschr. f. Biologie, 1879, xv, 425.

instead of 12.3, and with this the calculated surface areas of Meeh's three children were nearly the same as those actually measured. But when either of these constants is used to calculate the surface area of infants of different degrees of nutrition, the errors in certain instances may be extreme.

More recently Lissauer<sup>2</sup> has pointed out that either of these constants is too large for any but well-nourished children, and sometimes even for these. On the basis of twelve measurements of his own, almost all on poorly-nourished children, he has proposed 10.3 as a constant. While it is true that Meeh's formula with the constant 11.9, which has been used by Rubner and Heubner, Schlossmann and Niemann, is generally accurate for well-nourished children—but not always, as an error of 15 per cent. in one instance shows—it is very inaccurate for poorly-nourished children; and yet it has been used to calculate the surface area of all those infants with whom these authors have experimented, well-nourished and poorly-nourished alike. It is apparent that a formula is required that will have accuracy and elasticity so that it may be applicable to infants of all degrees of nutrition. Simplicity of calculation is also to be desired.

To this end we have constructed a formula of the  $y = mx + b$  form, using the data supplied by Meeh and Lissauer. We have employed the weight as the only variable in the formula, as it is apparent from a study of the figures given by Meeh and Lissauer that the length and the circumference of the chest bear no necessary relationship to the extent of surface. It is not, therefore, imperative to introduce them into a formula as Miwa and Stoeltzner<sup>3</sup> have done, with resultant complexity and no assurance of greater accuracy.

The weight and surface area were first plotted on a chart similar to the one shown in the illustration, and a curve drawn which appeared to represent in the best way the conditions. This curve, by its distance from the axes OX and OY, represents an average of the observed data, so that when drawn to the proper scale, the point on the curve or line representing any known weight of child may be marked on the chart and the corresponding area read off directly. Thus, if we have an infant weighing 7,000 grams, and we desire to know his surface area, we find where the 7,000 gram line intersects the curve. Carrying this point horizontally to the left we find that it intersects the OY axis at a point corresponding to 4,100 square centimeters. The small circles on the chart are indicative of the fourteen observations given in the tables. The curve was drawn as nearly as possible to all these points, so that the average distance from any point would be as small as possible.

2. Lissauer: *Jahrb. f. Kinderh.*, 1903, lviii, 392.

3. Miwa and Stoeltzner: *Ztschr. f. Biologie*, 1898, xxxvi, 314.

In the formula  $y = mx + b$ , which is the algebraic representation of this form of curve,  $x$  and  $y$  represent the abscissas and ordinates of the curve,  $b$  represents the distance along the  $Y$  axis from the origin to where the curve intersects the  $Y$  axis, and  $m$  represents the tangent of the angle that the curve makes with the  $x$  axis.

In this formula,

$y$  = surface area of child in square centimeters

$x$  = weight of child in grams

$m = 0.483$

$b = 730$

Having these last three quantities, it becomes possible to obtain the  $y$  or surface area by simple computation;  $b$  was read directly from the chart, and  $m$  was obtained by dividing 5,560—730 by 10,000.

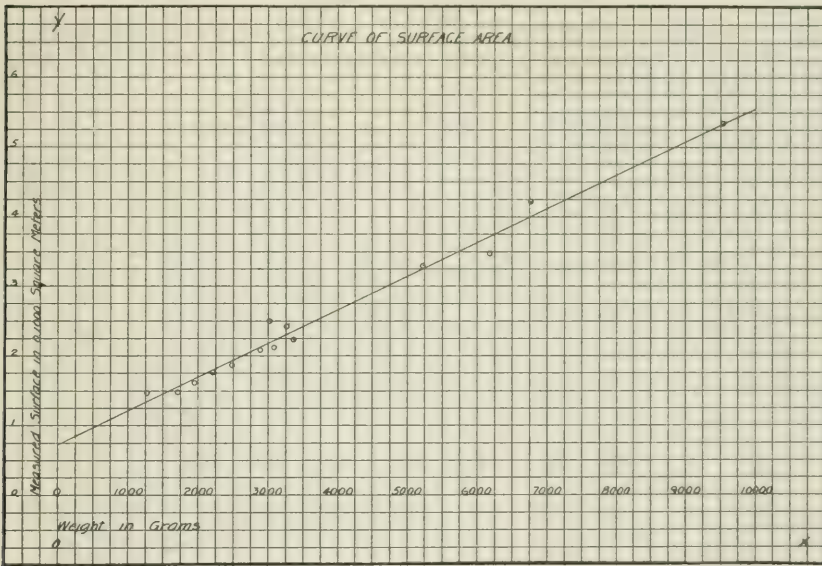


Chart showing weight and surface area determined as explained in the text.

This formula has the following advantages as compared with those of Lissauer and Meeh:

1. Accuracy.
2. Applicability to all conditions of nutrition.
3. Simplicity.
4. Elasticity.

1. The only accurate measurements of infants have been made by Meeh and Lissauer. They employed different but painstaking methods, and there is no reason to question the reliability of their results. They used, however, different types of children. Meeh was anxious to obtain



a formula accurate for all ages of normal individuals; Lissauer, on the other hand, measured with one exception only poorly-nourished and emaciated infants.

Meeh used millimeter paper laid on marked portions of the body and also accurately weighed paper for determining such areas as those of the nails. The extremities, fingers and toes were wound with circular strips. Lissauer measured cadavers by putting a colored adhesive material on the skin, pressing paper against the surfaces, and measuring exactly the stained portions after they had been removed. For infants between the ages of 6 and 435 days, there are available fifteen sets of observations obtained by these experimenters. One of these sets seems to be so decidedly abnormal that it should not be considered in the construction

No.	Surface sq. cm.	Weight, g.m.	12.3 $1/W_L$		11.9 $1/W_L$		10.3 $1/W_L$		$y=mx+b$	
			Error %		Error %		Error %		Error %	
			+	-	+	-	+	-	+	-
1	1462	1280	1450	0.8	1403	4.0	1215	16.9	1348	7.78
2	1482	1730	1773	19.2	1715	15.7	1485	0	1566	5.66
3	1610	1960	1928	19.6	1864	15.8	1613	0	1677	4.16
4	1768	2220	2081	17.7	2013	13.8	1742	1.5	1803	1.98
5	1866	2500	2266	21.4	2192	17.4	1897	1.7	1940	3.97
6	2092	2900	2501	19.6	2420	15.7	2095	0	2132	1.91
7	2116	3100	2615	23.6	2530	19.6	2190	3.5	2229	5.34
8	2230	3370	2764	24.0	2675	20.0	2315	3.8	2360	5.62
9	2420	3270	2710	12.0	2622	8.3	2269	6.2	2311	4.51
10	2595	3020	2575	2.8	2490	0.8	2150	14.1	2190	12.55
11	3292	5230	3706	12.6	3556	8.9	3103	5.7	3260	0.97
12	3470	6180	4142	19.3	4007	15.5	3469	0	3715	7.07
13	4222	6766	4310	2.1	4260	0.9	3685	12.7	4005	5.15
14	5345	9514	5530	3.5	5350	0	4630	13.4	5330	0.28
Total	35880		40349	12.4	39127	9.0	33858	5.7	35866	0

Table showing surface area of infants obtained by different formulas as compared with results obtained by actual measurement.

of a formula that is intended to express the results obtained in general form. The other fourteen are herewith tabulated in a comparative table showing the relative accuracy of the various formulas, namely, Meeh's, Rubner and Heubner's, Lissauer's and the one herein proposed. It will be observed that the gross error for the fourteen cases compares as follows:

Per cent.

Meeh ..... 12.4

Rubner and Heubner..... 9.

Lissauer ..... 5.7

$Y = mx + b$  ..... 0.



whereas the individual calculations show less departure from and greater consistency with the observed facts by means of the new formula than with any of the others.

2. The tables also demonstrate that the formula  $y = mx + b$  gives trustworthy results for all classes of children, the well- and the poorly-nourished, while the other formulas that have been proposed are not accurate in this respect. Thus Meeh's, and Rubner and Heubner's are fairly satisfactory for well-nourished children, but are very bad for the poorly-nourished; while almost the exact opposite may be said of Lissauer's.

3. By the other formulas it is necessary to take the cube root of the square of the weight of the child, multiplying this by an arbitrary constant, in order to obtain the desired area. In contrast with this, a simple multiplication and one addition are all that is required. A still simpler method of computing is by direct readings from a readily constructed chart, such as the one herewith presented, abscissas representing the weight in grams, and ordinates the desired areas in square centimeters.

4. This formula is constructed from the data at present available and can readily be applied to any future observations that may be made. No elaborate acquaintance with mathematics is necessary for this purpose. Future data may be plotted on this chart, and if it seems desirable to establish another curve to fit the then existing facts, the same can be done at sight and the new constant computed at a moment's notice. It should be mentioned in this connection that many more precise measurements on infants are needed in order satisfactorily to determine the average line. It is expected that with further observations, it will be necessary to alter this line somewhat, but the method of constructing the formula will still be the same and at the present time the formula is the most exact of those that have been proposed.

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# PROGRESS IN PEDIATRICS

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## THE DIAGNOSIS AND TREATMENT OF ENLARGED THYMUS

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In the vast majority of cases of enlarged thymus we are dealing with a simple hyperplasia of the organ. For almost a century the literature has been filled with discussions of enlarged thymus, and just at present the problems of thymus physiology and pathology are being studied by numerous investigators from various viewpoints. The present paper limits itself to a consideration of the diagnosis and treatment of simple hyperplasia, necessarily leaving untouched any extended consideration of moot points in thymus physiology and pathology.

Among the rarer causes of enlarged thymus, primary tumors, especially lymphosarcoma, carcinoma and dermoid cysts must be mentioned. It is known that lymphoid infiltration of the thymus occurs in leukemia. Tuberculous infection has been reported and syphilitic lesions have been observed quite a few times. It is worthy of note that children with congenital syphilis not infrequently show a persistent thymus. Indeed, Vacher<sup>1</sup> is of the opinion that syphilis as such may be one important cause of the persistent thymus, even though the gland shows no specific lesions.

### HISTORICAL

For nearly a century, to be exact, since the publications of Kopp in 1829, it has been known that a persistent or an enlarged thymus could cause disturbances of respiration. Indeed, our first description of thymic asthma came from Kopp. And it is noteworthy that his view that enlarged thymus could cause a true tracheostenosis with resulting compression disturbances, is to-day held by the majority of observers. The monograph of Friedleben appeared almost thirty years after Kopp's paper. Friedleben absolutely denied the possibility of mechanical compression of the trachea by an enlarged thymus, in fact, denied the existence of thymic asthma. And Friedleben's views were accepted until almost the close of the nineteenth century. Then Grawitz and Paltauf called attention anew to questions of thymus pathology. It was Paltauf who came to the conclusion that enlargement of the thymus constitutes

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1. Vacher: Hypertrophy of the Thymus in Syphilitic Children. Thèse de Paris, 1911.

but one manifestation of an abnormal constitutional state. He found that in his cases of sudden death without apparent cause, there was not only an enlarged thymus, but in addition a hyperplasia of the entire lymphoid apparatus. The chief characteristics of the abnormal constitutional state, to which Paltauf gave the name of status lymphaticus, may be thus briefly summarized:

General enlargement of the lymph-node groups in various parts of the body, hypertrophy of the tonsils, of the follicles at the base of the tongue and of the intestinal follicles, enlargement of the spleen and its follicles and the presence of a thymus larger than usual, or a persistent thymus at a time of life when normally the thymus has atrophied.

#### STATUS LYMPHATICUS

In addition there is a hypoplasia of the circulatory apparatus, narrowing and thinning of the walls of the aorta and smaller vessels, with, at times, degeneration of the heart muscle. The individuals are of pale, pasty habitus, and in older patients the blood-picture of chlorosis is constant. Whether we accept Paltauf's lymphatico-chlorotic constitution, or status lymphaticus, as a clinical entity, or not, it must be admitted that in many cases there may be a simple hyperplasia of the thymus without the concomitant signs of status lymphaticus. This fact adds not inconsiderably to the difficulties of diagnosis. At the outset it must be noted that enlarged thymus need not produce any symptoms whatever. The large number of sudden deaths in apparently healthy children, with cause of death enlarged thymus, would suggest this immediately. It is known that hyperplasia of the thymus is very commonly found in association with Graves' disease in adults. Thus Matti (quoted by Crotti<sup>2</sup>) found 133 cases of hyperthyroidism in which post mortem had been held, and in ninety-eight cases (74 per cent.) hyperplastic thymus was found.

Intercurrent affections, notably the acute infectious diseases, often light up pressure effects of an enlarged thymus hitherto unsuspected. Thus in a case recently under observation a child who had been perfectly normal, apparently, was brought to the hospital after an attack of whooping-cough with the typical picture of thymic asthma. *Post mortem* a hyperplastic thymus was found.

#### DIAGNOSTIC SYMPTOMS

Nevertheless, in the majority of cases certain definite symptoms and clearly defined signs permit the diagnosis of enlarged thymus to be made *intra vitam*. The symptoms of enlarged thymus are three — dyspnea, either continuous or remittent, suffocative attacks and stridor.

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2. Crotti: Thymic Tracheostenosis. Jour. Am. Med. Assn., Feb. 22, 1913.



The first diagnostic symptom to be noted, because it is the one most commonly present, is dyspnea. This dyspnea may be either permanent or intermittent. In his recently published monograph on the surgery of the thymus, Olivier<sup>3</sup> uses this symptom as a means of classification of cases.

The continuous form of dyspnea is the type most often seen in very young infants. The respiratory difficulty increases until the child has a suffocative attack, accompanied by intense cyanosis. The attacks are repeated with greater or less frequency, and death may occur during one of them. Between the attacks the dyspnea is continuous.

In the intermittent forms, children apparently quite normal, and usually several months of age, are suddenly seized with suffocative attacks accompanied by intense cyanosis, usually associated with convulsive movements of the extremities, followed after a few moments by a return to an apparently normal state. The intervals between the attacks, at first considerable, tend to become constantly shorter. Variations and gradations of the two forms are common, and have been frequently described.

The second symptom of frequent occurrence is stridor. This is usually inspiratory, though in extreme dyspnea an expiratory stridor is sometimes heard. In some cases the stridor is present from birth some time before even the dyspnea.

Now there can be no question of the very frequent association of congenital stridor and enlarged thymus. But it is surely not correct to assume, as do Haerttel<sup>4</sup> and Hochsinger,<sup>5</sup> for instance, that congenital stridor is always due to enlarged thymus.

Refslund and Koplik have shown that in certain cases of congenital stridor there is a peculiar malformation of the superior opening of the larynx. "The epiglottis has a gutter or beak-like form and is folded in the middle line." (Crotti.<sup>2</sup>)

Again, Lees and Thomson have shown that occasionally congenital stridor is due solely to incoordination of the vocal cords, the result of muscular imbalance. The diagnosis of enlarged thymus is thus certainly not justified on the find of congenital stridor alone, though the presence of this symptom should in every case awaken suspicion, and lead to careful physical examination.

This should include as a matter of routine, the search for evidence of the nasopharyngeal lymphoid ring, and particularly of the follicles at the base of the tongue. There has been much discussion as to the possibility

3. Olivier: *Anatomie topographique et chirurgie du thymus*. Steinheil, Paris, 1911.

4. Haerttel: *Zur Frage d. Thymustode*. Dissertation. Greifswald, 1911.

5. Hochsinger: *Stridor Thymicus Infantum*. Vienna, 1904.



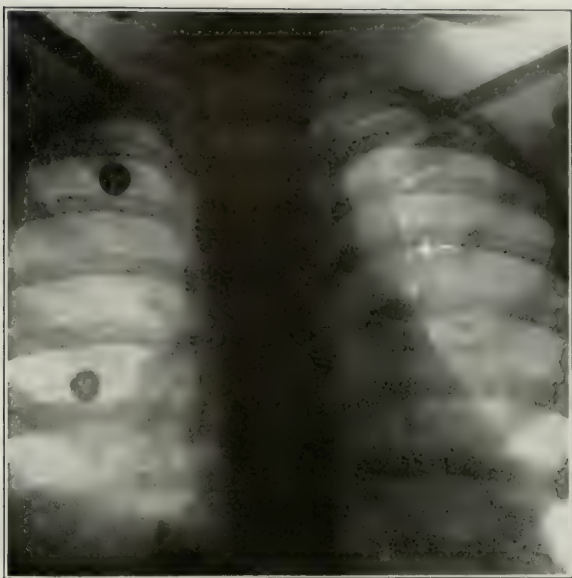


Fig. 1.—Enlarged Thymus. Broadening to left.

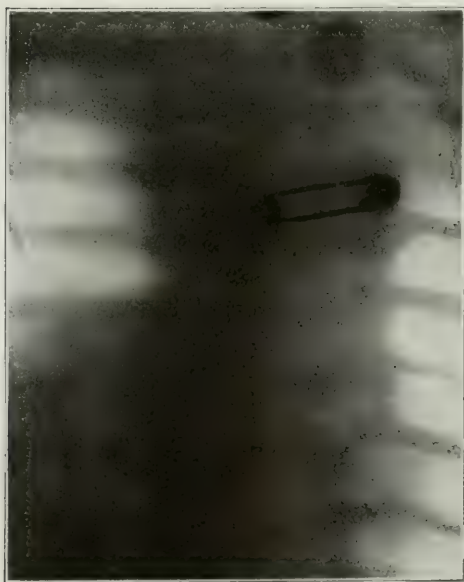


Fig. 2.—Enlarged Thymus. Broadening to right.

of actually diagnosing the presence of the enlarged thymus itself, but with the means at our command to-day, there can be no question of our power to do so.

#### PHYSICAL SIGNS

The physical signs of enlarged thymus are these: Detection of a mass in the jugulum by palpation, enlargement of the area of thymus dulness on percussion, the demonstration of tracheostenosis by bronchoscopic examination, or intubation, a special blood-picture, and finally the special type of thymus shadow as demonstrated by the *x*-ray.

In some cases palpation in the jugulum reveals the presence of a soft tumor, to be felt best during expiration. Attention was first called to this point by Rehn, but it must be admitted that it is an uncertain sign at best. This holds good also with reference to the bulging of the manubrium,<sup>6</sup> a sign surely absent in the majority of cases of enlarged thymus.

Percussion yields definite information of great value. Sahli<sup>7</sup> and Blumenreich<sup>8</sup> have formulated the principles for outlining the thymus by percussion. Blumenreich came to the following conclusions as the result of his studies: In young children there is a definite form of thymus dulness in the shape of an irregular triangle or truncated cone, whose base is the sternoclavicular junction and whose apex is the second rib. The sides extend but very slightly beyond the margins of the sternum, slightly more on the left than on the right side. Dulness extending more than 1 cm. on either side, concealing the note of pulmonary resonance between the heart dulness and the normal area of thymus dulness, shows, in the absence of other causes, an enlarged thymus.

Simply engorged lymph-nodes in the anterior mediastinum cause no dulness, while caseous nodes do. An important point to be noted is that dulness directly continuous from thymus to heart is always significant. Recently, Boggs<sup>9</sup> has claimed that the thymus dulness is movable, depending on whether the neck is flexed or extended, the difference amounting almost to an interspace. Personally, I have not been able to convince myself of this movable dulness, and quite recently Park and McGuire<sup>10</sup> have shown the incorrectness of Boggs' views, as the result of their anatomical studies. It may be remembered that Jacobi has claimed that the thymus is movable in the anteroposterior direction and that he has suggested percussing the thymus site with the child on its back and then

6. A. Mettenheimer: *Jahrb. f. Kinderh.*, xlv, 55.

7. Sahli: *Topograph. Percussion im Kindesalter*. Bern, 1882.

8. Blumenreich: *Ueber die Thymus Daempfung*. *Virchows Arch. f. path. Anat.*, 1900, cix, 35.

9. Boggs: *Percussion Signs of Enlarged Thymus*. *Arch. Int. Med.*, Nov. 15, 1911.

10. Park and McGuire: *Arch. Int. Med.*, Sept. 15, 1912.

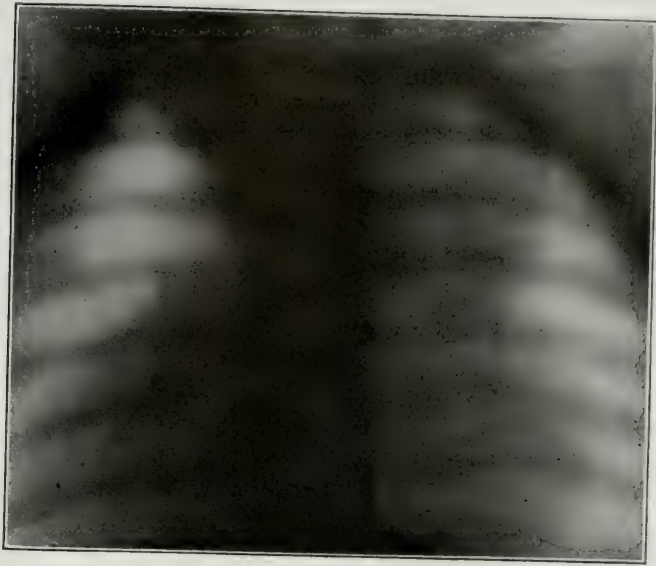


Fig. 3.—Enlarged Thymus. Broadening to right.

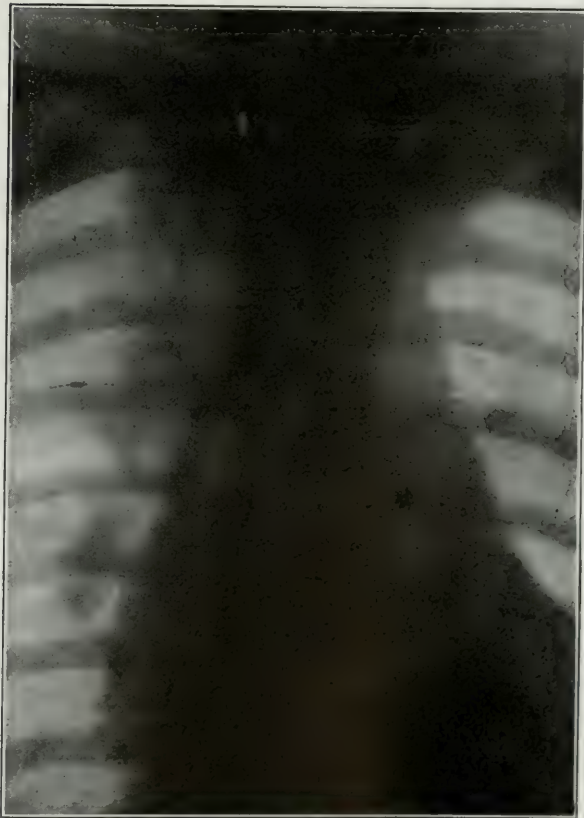


Fig. 4.—Enlarged Thymus. Cap.

percussing the area again from underneath with the child held face downward. So far as I know, there has been no confirmation of his findings of thymus motility in the anteroposterior direction.

#### DIAGNOSTIC METHODS

Basch and Rohn<sup>11</sup> have recently devised a special instrument for the percussion of the thymus. They claim that by its use in combination with auscultatory percussion and friction it is possible to obtain a more exact estimate of the size and condition of the thymus than has hitherto been the rule.

Recently the bronchoscope has enabled skilled observers to demonstrate the existence of a tracheostenosis in certain cases of enlarged thymus. This diagnostic method (first employed by Jackson), is, however, of limited application only, owing to the difficulty of laryngoscopic and bronchoscopic examination in children. Intubation has occasionally led to the diagnosis of enlarged thymus, as in Rehn's first operative case, where the long tube had demonstrated the presence of obstruction low down in the trachea. In cases of enlarged thymus in association with status lymphaticus, the blood-picture may be of diagnostic value. Thus in a case reported by Rachford<sup>12</sup> in a child 1½ years old, the differential blood-count showed a total lymphocytosis of 72.8 per cent. with the general blood-picture of chloranemia. Naturally, in older children a marked lymphocytosis is of greater diagnostic import than in young infants.

The diagnosis of enlarged thymus has, however, been simplified very greatly of late by the means of the *x*-ray. At the outset it should be noted that for this diagnostic work, especially in young infants, high power machines, taking almost instantaneous pictures, are essential. With the slower machines the shadows are often so blurred, owing to movements of the child, as to greatly diminish their diagnostic significance. Great emphasis is laid on this point by Lange of Cincinnati, who has had a very considerable experience in thymus radiography. Since the appearance of Hochsinger's monograph,<sup>5</sup> the use of the *x*-ray as a diagnostic method in enlarged thymus has become universal.

The *x*-ray shadow of enlarged thymus is a wide median one. In some cases the broad shadow continues up directly from the heart shadow, in others the thymus shadow appears like a broad cap superimposed on the shadow of the heart and vessels. It must be admitted that a broadening of the shadow above the heart is not always due to enlarged

11. Basch and Rohn: Physical Evidence of the Thymus. *AM. JOUR. DIS. CHILD.*, February, 1912, p. 82.

12. Rachford: *X-Ray Treatment of Status Lymphaticus*. *Am. Jour. Med. Sci.*, October, 1910.



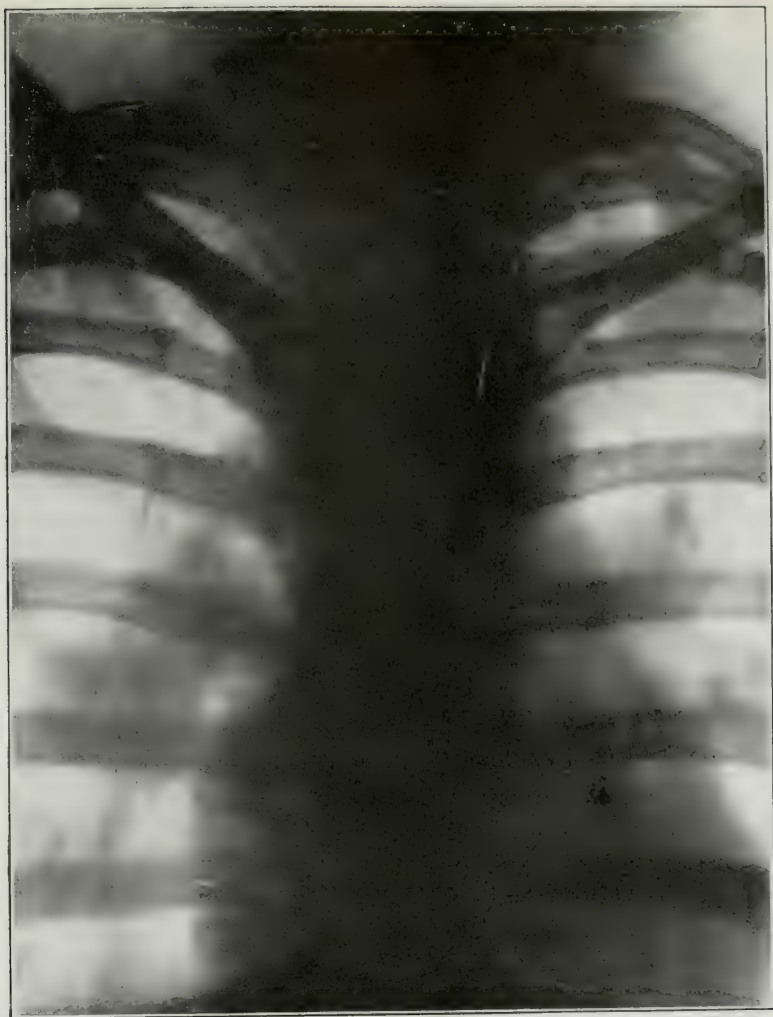


Fig. 5.—Enlarged bronchial glands. Right hilus.

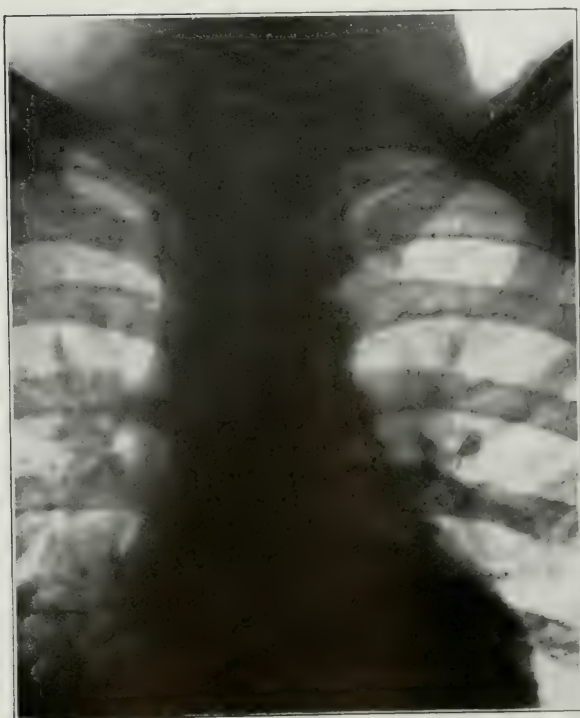


Fig. 6.—Glandular hilus. T. B.

thymus. In a careful study of the interpretation of the thorax radiogram in the nursling, Benjamin and Goett<sup>13</sup> point out that a broadening of the shadow to the right may at times be due to the large vessels, especially the vena cava superior. But, as they note, this cannot hold good when the larger part of the shadow falls to the left of the vertebral column.

Ferrand and Chatelin<sup>14</sup> find that the thymus and heart give a distinct sharp median shadow. Enlarged bronchial glands give an extra median shadow, separate from the heart shadow and not connecting with it. This latter point is of importance. Myer<sup>15</sup> has also called attention to it. There does not appear to be any question as to the diagnostic value of the *x*-ray in many cases of enlarged thymus. But even as experienced a radiographer as Lange expressly insists that in certain cases, especially if the gland be increased in size laterally without augmentation of its anteroposterior diameter (the large flat thymus), the *x*-ray picture may not be conclusive. As has been well said: "Where the *x*-ray evidence is positive, it is of real value in diagnosis, but when it is negative it is not to be considered as final."

#### TREATMENT

Turning next to the question of treatment, it should be said at the outset that any discussion of the therapy of enlarged thymus must necessarily include some consideration of the method of production of symptoms. It hardly seems possible to deny that mechanical compression must play a very decided rôle. At the superior opening of the thorax of a young child, the so-called critical space of Grawitz, the anteroposterior diameter measures only 2 cm. As a rule, the hyperplastic thymus is more than 2 cm. thick itself, and must compress trachea, esophagus and the large vessels and nerves. But even granting that direct or indirect pressure cannot explain all the symptoms, and assuming the correctness of the view of toxemia from excessive internal thymic secretion (Svehla's hyperthymization), the fact remains that it is the enlarged thymus which gives rise to the threatening symptoms, or is the source of danger to the child. Drug treatment is absolutely of no avail; indeed, it has long been recognized that medicines had no power to relieve thymic asthma.

#### SURGICAL TREATMENT

Within recent years surgical intervention has therefore been sought, the first operation having been done by Rehn in 1896. This first operation (exothymopexy) consisted in elevating the thymus from behind the

13. Benjamin and Goett: Interpretation of the Thorax Radiogram in the Nursling. *Deutsch. Arch. f. klin. Med.*, 1912, cvii, 107.

14. Ferrand and Chatelin: Value of X-Ray in the Diagnosis of Enlarged Thymus. *Bull. Soc. Pédiat. de Paris*, 1911, p. 164.

15. Myer: Status Lymphaticus. *Wien. med. Wchnschr.*, 1912, p. 1181.

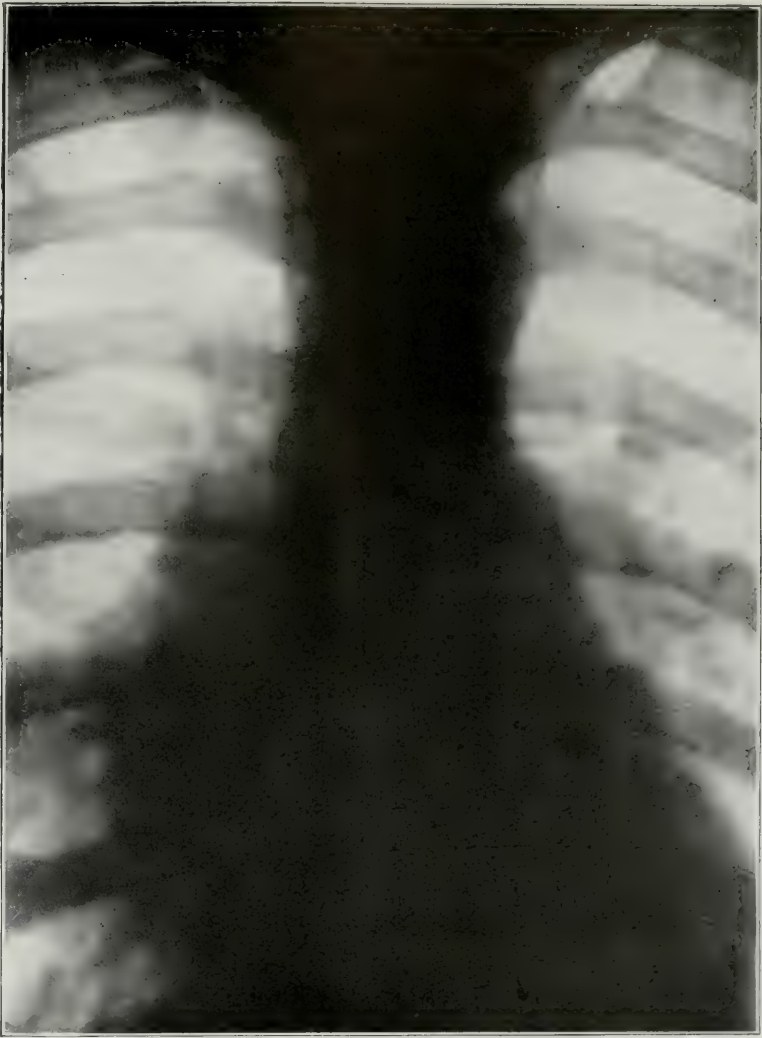


Fig. 7.—Glands at right heart.

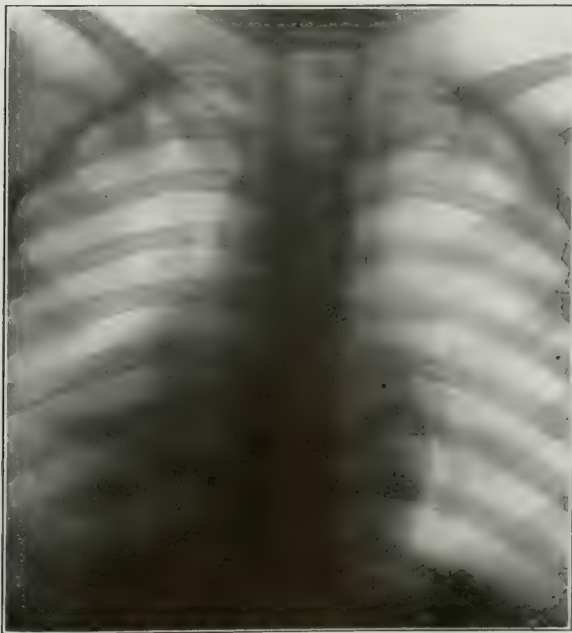


Fig. 8.—Congenital heart. (Pulmonary stenosis.)

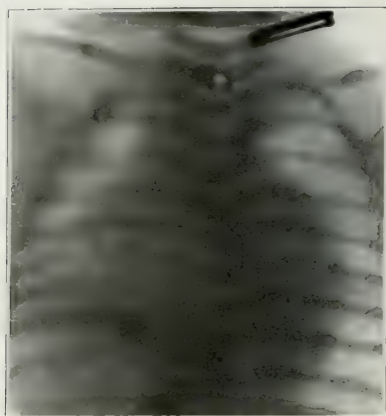


Fig. 9.—Congenital heart.



Fig. 10.—Pericarditis with effusion.



sternum and fastening it to the tissues of the neck or top of the sternum. The results of this operation were not good, and of late it has been superseded by the operation of removal of the gland (thymectomy).

The technic of this operation was worked out by French surgeons, especially Veau and Olivier.<sup>16</sup> The latter has published an exhaustive



Fig. 11.—Fibroid mediastinitis. One lung stone.

monograph on the topographic anatomy and surgery of the thymus. A collection of all reported operative cases together with a most excellent résumé of the entire question has just been published by Parker.<sup>16</sup> Of

16. Parker: Surgery of the Thymus — Thymectomy. *AM. JOUR. DIS. CHILD.*, February, 1913.

the fifty patients operated on, seventeen died, showing a mortality of 33 $\frac{1}{3}$  per cent. Even excluding some of the fatal cases, as Parker does for good reason, the fact remains that the mortality of the operation is high. Again, aside from the danger of the operation itself, it seems probable, in the light of recent research that the removal of all, or even of a greater part of the thymus may be fraught with grave danger to the subsequent development of the individual. The complete removal of the thymus during the period of its functional activity has been followed in the lower animals (rabbits, guinea-pigs, dogs) by very marked changes

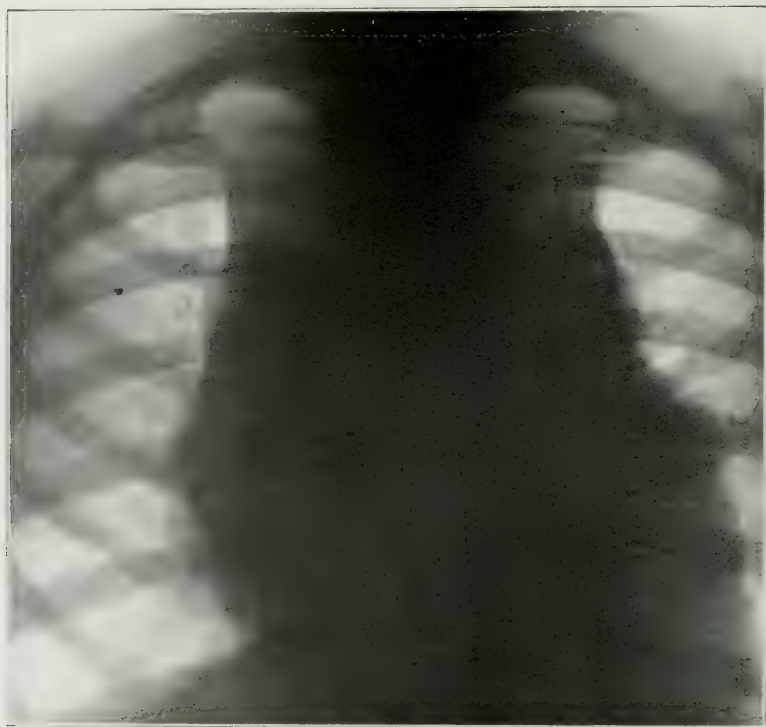


Fig. 12.—Lymphosarcoma. (Mediastinum.) Before treatment.

in the central nervous and osseous systems and in general development. While the animals have survived the operation itself, death has subsequently occurred in many instances under circumstances leaving no room for doubt as to the rôle of the thymectomy in its production. The experimental evidence of a good many observers is unanimous on this point, and the work of Basch,<sup>17</sup> Lucien and Parisot,<sup>18</sup> Klose<sup>19</sup> and Matti<sup>20</sup> gave

17. Basch: *Jahrb. f. Kinderh.*, 1906, lxiv, 1908, lxvii.

18. Lucien and Parisot: *Arch. de med. exper.*, 1910, No. 10.

19. Klose: *Arch. f. Kinderh.*, 1910, lv.

20. Matti: *Mittheil. a. d. Grenzgeb. d. Med. u. Chir.*, xxiv, Nos. 4 and 5.

21. Heinicke: *München. Med. Wehnschr.*, 1903, p. 2090.

identical results. Parker admits that the evidence is "strongly suggestive" that the thymus gland is absolutely necessary to life and normal development in the earlier stages of growth, but feels that its operative removal in the young human subject, so far as present evidence has shown, is not fraught with danger so far as subsequent development is



Fig. 13.—Lymphosarcoma. (Mediastinum.) After treatment.

concerned. And this because the gland is usually not completely removed. In the light of unanimous recorded experimental evidence concerning the effects of thymectomy on lower animals, this assumption certainly does not seem justified. We come now to the consideration of the x-ray treatment of enlarged thymus.





Fig. 14.



Fig. 15.



Fig. 16.



Fig. 17.



Fig. 18.

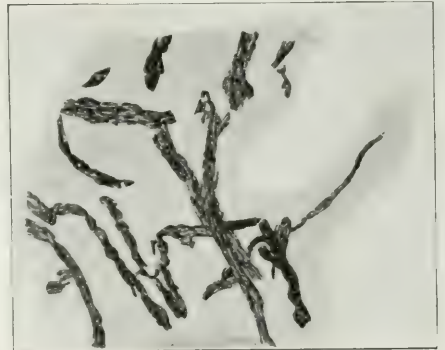


Fig. 19.

Figs. 14, 15, 16, 17, 18, 19.—Artificial Thymus Involution. (Rabbit.)



## ROENTGEN THERAPY

In 1903, Heinecke<sup>21</sup> published his studies on the effects of the *x*-ray on lymphoid tissues. He exposed young animals to the *x*-ray on successive days, then later killed the animals and studied the changes in the lymphoid structures. He found that the spleens of the animals showed



Fig. 20.—Rabbit Spleen. Normal.

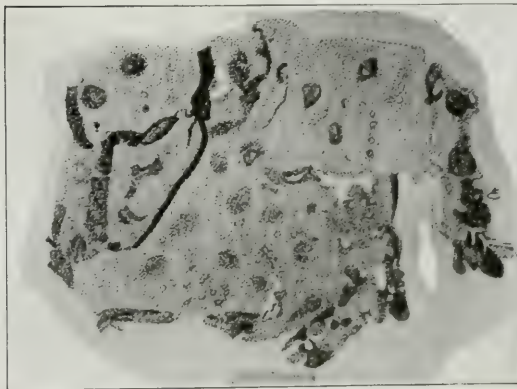


Fig. 21.—Rabbit Spleen. After treatment of the thymus region by the *x*-ray.

marked changes: increase of pigment, disintegration of cells, reduction in size of the malpighian follicles and rarefaction of the cellular elements. Analogous changes were found in all the lymph-node groups of the body, and, in very young animals, in the thymus. He suggested that it might

be possible that in the human being analogous changes might occur without skin reaction. In 1904, I had under observation a typical case of status lymphaticus with a greatly enlarged thymus in a 2-months old infant. The suffocative attacks were very severe, with dyspnea and cyanosis constant. In view of the desperate character of the case, the parents consented to allow the use of the *x*-ray, though, of course, no promise of relief could be held out. Twelve exposures in all were given, over a period of one month. The improvement was rapid, the suffocative attacks ceased, the thymus dulness became normal. The subsequent development of the child was absolutely normal, and at this writing the child is in perfect health. This was the first case of enlarged thymus successfully treated by the *x*-ray. Its publication was purposely delayed until 1907, in order that there could be no question of the result.<sup>22</sup>

Since this time, experimental studies by a number of investigators have demonstrated that it is possible to induce involution of the thymus by the *x*-ray. Aubertin and Bordet,<sup>23</sup> Rudberg,<sup>24</sup> and more recently D'Oelsnitz and Paschetta<sup>25</sup> and Regaud and Cremieu<sup>26</sup> have studied the process of such artificial involution in detail. In order to formulate the technic of *x*-ray treatment in cases of enlarged thymus, Lange and I conducted a series of experiments on rabbits, and showed that it was possible to induce any degree of fibrosis of the thymus, from the very slightest to absolutely complete fibrosis.<sup>27</sup> Reference to the latter point will be had later.

From the clinical standpoint the results have been extremely satisfactory as the published reports show. Since the report of my first case, there have been reports by various observers, of cases successfully treated — Myers,<sup>28</sup> d'Oelsnitz,<sup>29</sup> Rachford,<sup>12</sup> Weill and Pehu,<sup>30</sup> Ribadeau-Dumas and Weill.<sup>31</sup> In addition, Lange<sup>32</sup> of Cincinnati has record of eight other successful cases, not all of which have been reported as yet.

22. Friedlander: Enlargement of the Thymus treated by the X-Ray. *Arch. Pediat.*, July, 1907.

23. Aubertin and Bordet: Action de rayons X sur le thymus. *Arch. des mal. du coeur et des vaisseaux*. June, 1909, p. 321.

24. Rudberg: Studien ueber Thymusinvolution. *Arch. f. Anat. u. Physiol. Supplement*, 1907, p. 123.

25. D'Oelsnitz and Paschetta: *Bull. Soc. pédiat. de Paris*, 1911, p. 462.

26. Regaud and Cremieu: Thymus Involution by the X-Ray. *Lyon méd.*, 1912, cxviii, No. 1.

27. Friedlander: Involution of the Thymus by the X-Ray. *Arch. pédiat.*, October, 1911.

28. Myers: *Arch. Pediat.*, August, 1908.

29. D'Oelsnitz: *Compt. rend. de l'Assoc. française de pédiat.*, 1910, pp. 239 and 246; *Bull. Soc. de pédiat. de Paris*, December, 1911, p. 471.

30. Weill and Pehu: *Lyon méd.*, December, 1911, p. 1448.

31. Ribadeau-Dumas and Weill: *Soc. méd. d. hôp. de Paris*, March 27, 1912; Weill: *Bull. Soc. de pédiat. de Paris*, October, 1912, p. 383.

32. Lange: Personal communication.

The attitude of one French surgeon, at this time, is also exceedingly significant. Veau<sup>33</sup> of Paris has to a large extent worked out the plan of operation of the intracapsular thymectomy. In Parker's collection of fifty thymectomies, he is credited with eleven of the cases, either alone or in consultation. At the meeting of the Paris Pediatric Society, held Nov. 12, 1912, Veau commented on Weill's paper reporting three additional cases of enlarged thymus successfully treated by the *x*-ray. He reported two successful cases of his own and added: "For over a year I have not done a thymectomy, and up to the present have never been disappointed in radiotherapy."

Including these two cases of Veau, there are thus twenty-five cases of enlarged thymus successfully treated by the *x*-ray. Some of these cases come in the category of the very severe, with life-threatening symptoms present. Yet the *x*-ray treatment has been uniformly successful; nor has a single untoward accident occurred. There have been no retardations in the development recorded. Contrasting the list of twenty-five cases successfully treated by the *x*-ray, with fifty thymectomies and a mortality of 33 per cent., it would seem justifiable to maintain that radiotherapy is decidedly preferable to surgical intervention. Any extended discussion of the actual technic of the application of the *x*-rays would be out of place in such a paper as this, but it may be permissible to note certain facts, elicited as the result of experimental study. Lange and I have found that intense fibrosis may be induced by a comparatively small number of exposures if they are given on successive days.

Thus in our work on rabbits we found that four exposures on successive days gave a greater degree of fibrosis than fifteen exposures over five and a half weeks. The shorter the interval between the treatments, the more marked the results obtained. When the symptoms of pressure from the enlarged thymus are very urgent, therefore, and when there is evidently very marked mechanical obstruction, the *x*-ray treatments should be pushed, being given on successive days, or even twice a day at first to get quick results. The results from the treatment are seen very promptly. After even the first treatment it is noted that the dyspnea is lessened and the suffocative attacks are less severe.

When the symptoms are not so urgent, treatment may be given at longer intervals. Clinically, it has been noted that the symptoms of thymic asthma, which gradually disappear under *x*-ray treatment, tend to recur after varying periods of time in some cases. This is doubtless to be explained on the basis of regeneration of the thymus after partial fibrosis has been induced. In such cases further courses of *x*-ray treatment are needed, and may be relied on to induce fibrosis again. Clinically, the dosage of *x*-ray can thus be regulated according to the neces-

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33. Veau: Bull. de la Soc. Ped. de Paris, November, 1912, p. 426.

sities of the case. The danger of loss of thymus function (as in the case of complete thymectomy) is thus obviated and the metabolic changes after thymectomy are averted.

Although in all of the cases, both experimental and clinical, particular care has been taken to see that only the region of the thymus should be exposed to the action of the *x-ray*, we have found that after the *x-ray* treatment, changes in spleen and lymph-node groups could be noted. In two cases of status lymphaticus, one of my own, and one seen with Rachford and reported by him, we found that after the treatment the spleen and the lymph-nodes were notably reduced in size, coincidentally with the shrinkage of the thymus. Experimentally, Lange and I have been able to show not only marked reduction in size of the spleens of our treated animals, but also change in the histologic picture of the spleen. This observation opens an interesting field of inquiry with reference to the relation of *x-ray* treatment of the thymus and its effects on the general lymphatico-chlorotic constitution.

In our later clinical work, Lange and I have used much stronger *x-ray* dosage than was employed at first. No ill effects from the rays have ever been observed. The harmlessness as well as the effectiveness of the treatment have been abundantly demonstrated. With the larger dosage as now employed, with the rapid succession of treatments, prompt results may be looked for, even in the very severe type of cases. Fewer treatments are needed. The involution may be pushed as far as necessary without the slightest fear of later developmental abnormalities.

The promptness of response to the treatment is very noteworthy, marked improvement being usually observed even in the severest cases after the first treatment.

With the modern methods of precision the diagnosis of enlarged thymus has become much easier; with the *x-ray* treatment, successful therapy is assured.

4 West Seventh Street.



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### ENGLISH CONFERENCE ON INFANT MORTALITY

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An English-speaking Conference on the Prevention of Infant Mortality will be held in Caxton Hall, Westminster, London, on Monday morning, Monday afternoon and Tuesday morning, Aug. 4 and 5, 1913. The meetings will be held under the auspices of the (British) National Association for the Prevention of Infant Mortality and The Welfare of Infancy under the patronage of the King and Queen, and will convene immediately preceding the opening of the International Medical Congress.

A tentative program has been issued by the committee which indicates that the papers will consist largely of medical opinion. The subjects treated will be:

The responsibility of central and local authorities in infant and child hygiene.

The administrative control of the milk-supply.

The necessity for special education in infant hygiene.

Medical problems in infant nutrition.

Antenatal hygiene.

The president of the conference will be the Hon. John Burns, M. P., president for the Local Government Board. The chairman of the English Executive Committee is Sir Thomas Barlow and the secretary, Miss J. Halford, 4 Tavistock Square, London, W. C.

The American committee, in charge of the part to be taken by the United States and Canada, will furnish information to those desiring to attend the conference.

Dr. Henry L. Coit, chairman, 277 Mt. Prospect Avenue, Newark, N. J.

Dr. Philip Van Ingen, secretary, 125 East Seventy-First Street, New York City.



# American Journal of Diseases of Children

VOL. 6

AUGUST, 1913

No. 2

## PANCREATIC INSUFFICIENCY \*

LANGLEY PORTER, M.D.

SAN FRANCISCO

A severe indigestion of acute onset and protracted course, characterized by the evacuation of bulky, pale-gray, greasy stools, occurs fairly often in early childhood. Marked wasting is a feature, as is the occurrence of periods of amelioration during the earlier months of the affection. The stools invariably contain a large amount of wasted fat which is excreted unsplit, and in the graver examples of the disease starches are passed undigested, and sometimes proteins even escape digestive action.

English writers have called this symptom group "Coeliac disease." Robert Hutchison has written a lucid clinical description of it, and in his paper he quotes opinions of Cheadle, Gee and Gibbons on the subject. Eustace Smith has also considered this symptom-complex at length in his lectures on "The Wasting Diseases of Children." The English writers seem inclined to attribute the fat waste to an unexplained diminution in the fat-absorbing powers of the celiac lymphatic system.

In America, Herter, searching for a type of possible onset for those cases of infantilism which he believed to be of intestinal origin, made a study of such cases which he describes as acute and subacute intestinal affections leading to infantilism. His account is worthy of reproduction:

### HERTER'S INFANTILISM

Such cases begin, for the most part, between the end of the first and the middle of the third year; they are characterized by diarrhea, usually without tenesmus, with an abundance of mucus but no blood. The diarrheal discharges are usually not frequent, while the loss of weight is not rapid—about one-half ounce daily—it may progress until the child is much emaciated. There is usually considerable flatulence. There is a moderate or marked fall in hemoglobin; the temperature is normal, or subnormal, the appetite is unimpaired. The disease lasts from three to six weeks and recurrences are very apt to occur. The carbohydrates are very badly tolerated and many relapses are certainly due to their incautious use. The urine gives intense reaction to indican and to aromatic oxyacids. Examination of the Gram-stained fields from the stool of a typical example of this infection shows it to consist almost wholly of Gram-

\* Read at the meeting of the American Pediatric Society, Washington, May, 1913.

\* From the Medical Department of Stanford University.

positive bacilli, presenting the morphological characteristics of the simple form of *Bacillus bifidus*. This organism can be readily cultivated; the *Bacillus infantilis* is obtainable from some, perhaps all, of the stools, and from the intestinal mucus it grows freely, sometimes almost alone when planted in fermentation tubes.

He further states that the very small number of Gram-negative bacteria to be seen in these fields is very striking. Herter's description of Gram-positive bacteria in the stools in such cases was corroborated by Pantón in two of Hutchison's series. Apparently Herter would consider the cases explained by enteritis due to invasion by unusual bacterial forms.

French authors, Carnot, Arragas and Vinas, have dealt with the same phenomena, and have referred the food waste and resulting starvation to a primary impairment of the pancreatic function. And it is significant to note that cases analogous to the infantilism described by Herter as of intestinal origin have been reported by Bramwell and by Rentoul, and by them considered as due to failure of the pancreatic function.

From the study of a number of such cases, three of which are here reported, it has seemed to me that the apparently conflicting opinions as to etiology can be brought into unionism.

#### DUODENAL ORIGIN

There is evidence to support the contention that the primary lesion in these cases is an infective duodenitis with a secondary invasion of the pancreatic ducts and the production of pancreatic insufficiency, and the assumption of this theory has suggested a therapeutic procedure for the severe cases that seems worthy of further trial.

The rôle of the pancreas in fat-splitting is so well demonstrated that there is no need to quote the various physiologists and clinicians who have written on this subject. There seems to be a general consensus of opinion that if more than one-third of the fat ingested appears in the stools unsplit — that is, in the form of free fats — or even if such a proportion carries material quantities of fatty acids, the steapsin of the pancreas may be considered to be either insufficient or inefficient.

This view is opposed by Vaughan Harley who holds, from the study of a case of pancreatic obstruction, and from experiments on depancreatized dogs, that when excess of fat appears in the evacuations, diminished absorption, rather than deficient splitting, is the lesion. He came to this conclusion because, in his cases, a small proportion of fat was absorbed, but a large part of the waste appeared as fatty acids and soaps. He further feels that the pancreas has some internal secretion, as yet undiscovered, which is active in the absorption and utilization of fat, and this view is borne out by the experiments of Gross and of Falta. It is well understood that pathologic conditions in tissues other than the pancreas can lead to a large waste of fat in the stools. In acute duodenitis with

jaundice, in certain diseases of the liver in which biliary secretion is suppressed, in chronic tuberculous mesenteric adenitis, and in any acute enteritis, stools bulky with wasted fat may be encountered.

Talbot, in an interesting paper on tuberculous mesenteric adenitis, reports but one case in which the bowel movements contained any large amounts of free fat or fatty acids. In the major number of his cases, the fat excess was in the form of soaps, and his observations coincide with my own and with those of most observers. These findings indicate that the fat has been split, but that the absorption is inadequate. The few reported cases that show deficiency of fat-splitting can be explained on the ground that there is a partial or complete blocking of the pancreatic duct by that group of glands which lies about the head of the pancreas, where inflammation or enlargement might affect the duct by contiguity.

An interesting description of the rôle of the pancreas in splitting and absorbing fat, with an account of an unusual case of steatorrhea persisting from birth in an otherwise healthy child, one of whose five brothers was similarly affected, is contained in a paper by Garrod. The author assumes an inborn failure of fat-splitting power on the part of the individual reported on.

It seems also to be clearly demonstrated that one of the three pancreatic ferments, the lipase, the amylase, or the alkali protease may be diminished in quantity or power, while the other two secretions of the gland are doing their work in a fairly normal manner. A paper by Gross discusses this subject fully in its relation to the adult pancreas, but there seems to be no adequate study of the difference between the secretory power of the young pancreas and that of age.

The fact that bacterial invasion of the pancreas happens through the ducts as well as by the blood-stream, by the lymphatics and by contiguity (especially from infected mesenteric glands), is one of the best demonstrated facts in medicine, for acute suppurative pancreatitis, which one hears of rarely in childhood, has been reported to have been produced by the colon bacillus, the streptococcus, the staphylococcus, by mixtures of these two organisms, by the pneumococcus, by the bacillus of Friedlander and in rare cases by the typhoid and paratyphoid organisms. Invasion is determined by two facts: 1. By the production of much mucus at the ampulla of Vater, which causes partial blocking. It has been shown that under such conditions of stagnation the bacteria, especially motile bacteria, can readily ascend any of the body's various ducts. Bond's work on ascending mucus currents is of particular interest in this consideration. He has shown that when epithelium is damaged, inert particles can ascend ducts lined with mucous membrane, and he has suggested that this is a common mode of ascending infection by bacteria. 2. The second



determining factor was pointed out by Carnot, who has made a thorough study of pancreatitis. He demonstrates that blocking allows pancreatic enzymes to act on the epithelium lining the ducts and to soften and destroy it, and so provides pabulum for the organisms imported from the gut.

As long ago as 1898, Arraga and Vinas, in a detailed study, showed that it is not rare to encounter a more or less complete blocking of the pancreatic duct of children, with invasion of the duct by intestinal bacteria. Herter has shown, however, that at the level of the upper portion of the duodenum there are normally very few or no bacteria, and that these, when they do occur, are not of the pathogenic type. The inference is, then, that any invasion of the pancreas is secondary to a duodenitis in the presence of unusual bacterial forms in the upper gut.

#### BACTERIOLOGY

The type of case that this paper deals with cannot, of course, arise from acute suppurative pancreatitis, but if the possibility of ascending infections be accepted, as it is by all those who have carefully studied the matter, it is conceivable that bacteria of low pathogenic power ascending the ducts under like conditions will give rise to low grade of inflammation, followed by fibrosis, greater or less in degree. As a matter of fact, this is just what does happen, and such conditions found post-mortem in the pancreas have been attributed to invasions by colon bacilli of low resistance, to the staphylococcus, and to other pathogenic germs whose powers to damage their host had been minimized by residence.

On the other hand, organisms whose virulence is never great may establish themselves in the intestine. In the condition of acute and subacute infection already referred to as described by Herter, fecal fields instead of showing the normal preponderance of Gram-negative bacilli of the colon group, exhibit a bacterial flora similar to that seen in the stained fields made from feces of normal breast-fed nurslings. That is, the bacteria in these fields present the morphological characteristics of the simple form of the *Bacillus bifidus*. In some of these cases, a bacillus described by Herter and Kendall as *Bacillus infantilis* is present. There is some doubt as to the exact position this organism should take, and even Herter was of the opinion that it might possibly be a form of the *Bacillus bifidus*. Herter was interested in these cases chiefly because of the likeness the intestinal flora showed to the flora he found in those cases of infantilism that he studied and grouped as of intestinal origin.

The study of the stools in the group of analogous cases reported by Dr. R. G. Freeman, showed that in some the same types of *Bacillus bifidus* were predominant, and in others, one case in particular, Welch's *Bacillus aerogenes capsulatus*, occurred in preponderance with no *B.*



*bipidus*: in another, it was found in company with the latter organism and other bacilli.

When one considers that although steapsin is obtainable from the intestinal mucous membrane and from many other tissues of the body, the possibility of another lesion than that of the pancreas must be admitted in the case of those patients who waste fat so considerably, but that the pancreas should not be involved is unlikely even if other tissues are at fault. As a matter of fact, the post-mortem records of Arraga and Vinas reveal that in children who have shown such clinical pictures, there has been invasion of the ducts with evidence of chronic inflammation around the ducts; they describe the pancreas in these cases as being remarkable for the diminution of its volume, its increased hardness, its toughness on section and for definite marking out of its lobules in which the normal differentiation is markedly exaggerated. They say that throughout the essential tissue minute areas of degeneration and hemorrhage are found dotting the lining membrane of the ducts, and that there is a great increase of viscid mucus within these ducts. They describe the microscopic picture in these words:

If we examine the duct of Wirsung at or near its entrance into the intestine, we are struck in many cases by the fact that the lining epithelium has almost disappeared. The wall of the duct is markedly thickened and is made up of fibrous striae surrounding collections of leukocytes. There is also in the new connective tissue a very marked increase in the number of blood-vessels, and these, for the most part, are unduly dilated. In the less severe cases, the process is not so advanced and we are able to see the epithelium in the process of degeneration; there is softening of the cells, with a fragmentation of the nuclei which gives rise to a poor staining reaction. Many of the cells are in the process of desquamation and are contributing to accumulations that block the ducts. A thorough examination shows that the degree of damage is proportional to the duration of the disease. From the finer ducts which have been attacked, widespread invasion of the parenchyma of the pancreas takes place, and is followed by a connective tissue increase. Following this increase of tissue, one finds secondary changes in the pancreatic acini, some of whose cells undergo softening, and others coagulation necrosis, with nuclei of lost contour, and poor staining quality. These lesions are most frequent in that portion of the pancreas neighboring the outlet of the duct of Wirsung. In those instances in which enteritis has been persistent and of long duration, a marked dilatation of the veins of the pancreas may be seen.

These authors look on the *B. coli communis* as the probable invader in these cases. They consider its motility as an important factor in aiding its entrance to the pancreas, but when we consider the work of Bond already referred to, there is no reason to doubt that any organism, motile or immobile, can invade the pancreas.

It seems perfectly reasonable, then, to assume that in the cases of patients whose stools show marked increase in free fat waste, definite depression of those digestive powers usually attributed to the pancreas, and in the stool a predominance of abnormal bacteria, the ducts of Vater,

and through them the pancreatic tissue, has been invaded by these abnormal organisms, and the pancreas has undergone an inflammatory reaction which has damaged the secretory power of the gland and impaired the digestive quality of its juice.

The autopsy of one of the cases here reported seems to warrant such an assumption, and the clinical findings in another also indicate the probability of this pathological complex. The fact that many of these patients automatically recover is no argument against this contention, because it is quite conceivable that certain mild cases may be due to the establishment in the upper intestinal tract of a bacterium that maintains itself in this region with difficulty. Unless invasion of the pancreas occurred very rapidly, such an organism would find that the body had adapted its protective powers in the way that happens so frequently when the colon bacillus invades the urinary tract. Again, following dietetic measures, or the use of saline or mercurial purges, inflammation in the intestine may be allayed, mucus accumulations obstructing the outlet of the ducts cleared away, and the conditions which favor invasion of the pancreas by bacteria changed. The fact, therefore, that many cases have improved on simple dietetic treatment, or after the use of mercurial purges, is perfectly in accord with the view of the etiology here set forth.

The following examples of cases met in practice will be used to emphasize the contentions made in this paper.

#### CASE REPORTS

CASE 1.—Stella S., aged 22 months; weight 17 pounds. At the age of 1 year she suffered from an attack characterized by frequent, loose bowel movements, without pain, tenesmus or fever. This attack lasted for about ten days and she had no more trouble until February, 1911, when she had a recurrence of the same conditions in a more severe form; this attack had lasted for about three weeks when the child was first seen on February 27.

*Physical Examination.*—The child was then wasted and irritable. Hair was ill-developed and she had a distended belly; no fluid was found in the peritoneal cavity. The tonsils were not enlarged; there was no clinical evidence of lues; the Wassermann test was negative. The stools were characteristic, bulky, grayish-white, greasy bowel movements. The attending physician stated that she had had very marked starch waste.

She was put on a diet of 800 calories a day, provided through dextrins, skim milk, gelatin, scraped beef or white fish, macaroni or rice, with green vegetables and fruits.

The report of the stool examination showed that on different occasions there was a great excess of free fat and fatty acids with some soaps; a moderate number of starch granules, both free and encapsuled were found. The blood showed 75 per cent. hemoglobin, 12,000 white cells, 58 per cent. lymphocytes, 42 per cent. polymorphonuclears; no parasites.

On July 20 there was no free starch in the stool; neutral fats and fatty acids were present in excess; the bacteria were predominantly Gram-positive; no colon bacilli.

August 29 a large amount of starch was being wasted; it seemed there was no fat in one examination, but the Gross casein method and Wohlgemuth starch test gave a very marked diminution in the amylase and protease of the stool.

September 6 there was a considerable excess of starch and of free fat; casein and starch digestion by the above methods was very much improved—from 100 units at the first examination, to 375 at the last. The child in the meantime increased in weight and well-being; her appetite improved and October 4 her weight was 24½ pounds. Since that time she has made a steady gain in weight and health and has shown no tendency to a recurrence. On the last examination of her evacuation by Dr. Alvarez, fourteen months after she was first seen, there was no excess of fat, free starch was not present, and the normal Gram-negative colon bacilli were reported as being predominant in the stool.

This is an example of a mild and temporary pancreatic insufficiency which is not at all uncommon to meet in infants of this child's age, and which, it seems probable, is due to a bacterial invasion of the intestinal tract and an ascending infection of the ducts of the pancreas. It is an upset which rights itself when under proper feeding conditions, the unusual bacteria give way to those normal to the small intestine, which under ordinary conditions are unable to grow with any amount of vigor so high up as the opening of Vater's duct. There are a number of cases in our history files which duplicate this in all its essential particulars.

The following case is an extreme example of the same condition:

CASE 2.—A. H. was first seen in his twenty-first month. Then he weighed 14 pounds, an increase of but 7½ pounds since birth. His mother's statement was that he had been breast-fed for the first four months, and that during this period he had gained one-half pound a week; from the fourth month he gained but little and at 9 months ceased to gain, but seemed contented and happy until during his tenth month he began to vomit; during the attacks he brought up at first food, and later large quantities of sour-smelling, bile-stained, watery material. There was then a period of improvement which lasted four months, although at that time he was on a diet that apparently contained about 5½ per cent. of fat. He then developed an alimentary intoxication, when he was seen by another physician who withheld all food save skimmed milk. Under this regime a slight improvement followed with a gain of a few ounces a week. At the age of 16 months he began to stand and was steadily gaining strength, up to his twenty-first month, when I first saw him in a vomiting attack similar to those already described.

*Physical Examination.*—The infant was found to be suffering from marked scurvy which rapidly disappeared when he was fed fruit juices. He was emaciated, with an exceedingly protuberant belly. Examination revealed nothing abnormal in nervous system, heart, lungs or abdomen, except marked distention, which was obviously due to intestinal gas. Neither spleen nor liver was enlarged; there was no fluid in the peritoneal cavity and no enlarged glands present. The blood showed no lymphocytosis, the hemoglobin was slightly diminished, no nucleated cells were present, but there were some alterations in the size and shape of the cells. The child vomited a large quantity of bile-stained fluid mixed with mucus and smelling of fatty acids. He would vomit from 1 to 2 quarts of this material daily during the attacks, which lasted from two to five days; during these periods the urine was scanty and concentrated. He had from two to three foul stools daily. When first seen these stools were scanty and composed largely of mucus; between the attacks of vomiting the stools were large and greasy, and contained large amounts of free fats and fatty acids. There was no starch reaction to iodine; no muscle fibers were found present; this examination was made some days after the child had been on a mixed diet of green vegetables, broth and scraped beef, with minimum amounts of



fat. The urine at this time and in subsequent examinations showed a heavy indican reaction, and Ehrlich's aldehyde reaction was positive, but neither albumin nor casts were found. On a mixed diet, with the exhibition of gray powder,  $\frac{1}{2}$  grain three times daily, the stools improved, the general condition was better and there was no further vomiting.

*Management and Course.*—In his twenty-eighth month the child suffered an attack of whooping-cough through which he passed uneventfully and from which he recovered without complications. After this he gained at the rate of about 1 pound a month until he weighed  $18\frac{1}{2}$  pounds. During this time no deficiency in the digestion of starch or protein was demonstrated by the Gross or Wolgemuth tests, but diminution in the pancreatic steapsin was to be inferred, as the fats were apparently entirely unsplit and unabsorbed. Unfortunately, no quantitative determination of the relation between the ingested and excreted fat was made. Under the most careful and searching clinical observation by me and by Dr. Charles Minor Cooper, no indication of any complicating disease could be determined; the digestive tract only could be implicated.

The child's appetite was extremely capricious and it was difficult to get him to take a sufficient amount of food. On two separate occasions there was a definite color change in Fehling's solution when boiled with the urine. The change did not occur immediately and there was no true precipitation.

In his thirty-second month there was a very marked acceleration of all the symptoms. The patient, who had been improving and was allowed some freedom in diet, was seized with a characteristic diarrhea, having four to five stools a day. These were fetid, fatty-acid odored, greasy, and under the microscope they showed quantities of unsplit fat. This in spite of the fact that the fat was limited in the diet. During this attack, for the first time, starch appeared unaltered in the stools and meat fibers were discovered undigested, although meat was given in the form of very thoroughly scraped beef. At this stage an emulsion of raw sheep's pancreas was given with apparent effect. The child improved in strength and digestive power and returned to a limited degree of comfort, and again began to gain in weight. A light attack two months later was checked, whether spontaneously or through the aid of the pancreas emulsion, one is not certain. Pancreon (Rhananier), which it was attempted to give this baby, was always vomited. During the period of pancreas feeding, the pancreatic nuclei were always passed undigested and could be seen in great numbers in the stool.

At all examinations the fields of fecal flora showed a preponderance of Gram-positive cocci and bacilli which were reported as not unlike Boas Oppler bacilli, but smaller. At that time we attached no importance to the presence of these organisms in the digestive tract.

When the child was within a month of completing his third year he again became the subject of an attack which proved fatal. At this time he was not under direct observation, but the mother, a very intelligent observer, declared that on several occasions he passed voluminous stools of tarry material, which description seemed to indicate hemorrhage from the intestine, although the autopsy records showed that no blood was found in the intestine after death.

*Necropsy.*—The child died at 7:15 p. m., Sept. 18, 1911. Autopsy was permitted, but was not done until noon of the following day. The autopsy records state that the post-mortem revealed a very wasted child, the body in marked *rigor mortis*. On opening the belly, the intestines were pale and moderately collapsed. The ascending part of the duodenum was hard and seemed fibrotic. No fluid in the peritoneal, pericardial or pleural sacs; retroperitoneal glands slightly enlarged, not inflamed. Liver slightly decreased in volume, somewhat hard, spleen normal; right kidney larger than the left. The pancreas lay across the spine as a hard cord about the size of the little finger, was pale in color, but did not tear easily. Unfortunately, no examination was made of the papilla of Vater nor of the condition of the ducts. No enlargement of the mediastinal



or bronchial glands was found. Lungs free from adhesion, pale in color, did not tear easily, left apex firm to the touch, but floated in water. Heart in systolic contraction, normal.

*Microscopic Examination* (by Dr. William Ophüls).—Pancreas showed increase in connective tissue of septa; slight interlobular increase; pancreatic tissue was fairly abundant and seemed normal in appearance; there were many islands of Langerhans. Kidney showed slight increase of connective tissue in cortex; tubules normal; glomeruli normal. Lungs showed some areas of collapse where lining epithelium was cubical; otherwise normal. No abnormal changes in the intestine. Diagnosis: Pancreatic fibrosis; slight interstitial nephritis.

CASE 3.—This paralleled the last described in all the features except outcome. B. J. When the child was 13 months of age her mother noticed an abnormal distention of the abdomen; a week later vomiting with fever ensued and lasted two days; the stools, four to six daily, were then gray, smooth and voluminous. When first seen she was 17 months old. It was related that she was losing weight steadily.

*Physical Examination*.—The child was moderately grown, poorly nourished, much wasted; abdomen distended, not very full in the flank; bimanual examination made under anesthesia per rectum disclosed no tumors and no enlargements of the viscera. Reflexes, heart, lungs and throat normal. Blood, 10,200 white cells with a normal differential count. Hemoglobin 65 per cent. Von Pirquet tuberculin test was negative. Stools showed abundance of fats and fatty acids, some soaps, meat fibers, starch, dextrin and nuclei. Bacteria, Gram-positive bacilli in predominance. Urine usually normal; on two occasions showed slight sugar reaction; occasionally gave a marked indican reaction; the stools showed a moderate Ehrlich's aldehyde reaction; on a number of occasions a slight trace of albumin was present; at several times a few granular and hyaline casts were seen. Acetone was occasionally found during periods of starvation, and the same Gram-positive bacterium that dominated the stool was found in the urine several times; this was probably due to contamination. During the pancreas feeding an enormous amount of uric acid was reported as being present in the urine.

*Course*.—The child went progressively from bad to worse, and no food was tolerated by the intestine until Loefflund's malt soup, prepared with skimmed milk, was tried, and even with this aliment undigested casein was present in the stools. The weight fell steadily until it was less than 10 pounds. The clinical picture of extreme starvation with irritability was most pitiful. During this time the stools continued to show the Gram-positive bacillus in practically pure culture.

*Bacteriology*.—Dr. Alvarez' report is as follows: Escheric stain shows almost pure culture of a Gram-positive bacillus, often slightly curved, not as long as the Boas Oppler (probably not *Bacillus bifidus*). Fermentation tube culture shows a large amount of gas with a strong odor. Sediment shows a large number of the Gram-positive bacilli seen before and large amount of proteins; no signs of *Bacillus bifidus*. Acid bouillon shows no growth in ferment tube.

Emulsion of raw pancreas was given without apparent effect on the digestion; in fact, the amount of fat contained in the pancreas seemed to make matters very definitely worse, and unsplit fat appeared in the stools. With the hope of stimulating secretin, hydrochloric acid was now given without any change in the stools. Shredded pig's duodenum was now used in the attempt to provide a secretin, but without success.

*Vaccine Treatment*.—Dr. Walter C. Alvarez, to whom I am indebted for the laboratory examinations in this case, suggested that the constant domination of the stool by a Gram-positive bacillus was presumptive evidence of the pathogenicity of this organism, and proposed that an autogenous vaccine be prepared

and given to the child. This was done. The report of the first culture of this organism is as follows:

Culture on agar shows very minute white colonies which are apparently pure culture of the Gram-positive bacillus. They grow occasionally as long threads, or again as diplobacilli. On bouillon, the Gram-negative organism predominates by far. Transplant from agar to agar shows marked change to a thick diplobacillus sometimes so short as to be a thick diplococcus in chains; a few are Gram-negative and some may have spores.

The vaccine was prepared from the agar culture and every third day was given to the child in increasing doses, beginning with ten million. Up to this time the reports of stool examinations showed absence of diastase, low trypsin and practically no fat digestion; diastase was also absent from the urine.

No change was observed in the child for five days, when a fair amount of diastase was reported as being present in both stool and urine. The next examination, five days later, showed that there was still an excess of starch in the stool, but more than the usual number of Gram-negative bacilli, although there was still a large number of Gram-positive organisms. Subsequent examinations showed variations, diastase increasing in the stool, and starch varying from none to a slight excess, in one instance a large excess; free fat, fatty acids and soaps decreased in quantity, although whole milk was added to the dietary.

Three months after beginning the vaccine treatment, after about thirty injections, there were very few Gram-positive bacteria present, and the stool contained considerable soap. Five months after the beginning of the treatment, after an unremitting improvement, the child was able to take a normal mixed diet with a moderate amount of fat without any excessive waste; the stools showed simply a high predominance of soap, no wasted starch and a normal bacterial picture. By this time the child weighed 21½ pounds and was apparently in good general health.

#### CONCLUSION

It may be concluded then, that in the group of cases characterized by waste of most of the ingested fat, with or without loss of the ingested starches and proteins, we are probably dealing with a bacterial invasion of the pancreas secondary to the presence of an abnormal bacterial flora in the small intestine. The material here presented is too scanty to expect conclusions drawn from it to be accepted as final; the paper is prepared with the hope that others may consider it worth while to investigate the condition from this point of view.

The question of the value of vaccines in such a condition is brought up because in one case the results following the use of a vaccine were so striking that it seems impossible that mere coincidence will explain them. It is not suggested that one certain organism is specific for this condition. It seems quite reasonable that any pathogenic bacterium, or even the colon bacillus, under abnormal intestinal conditions, may become the inciter of a pancreatitis which may lead to a suppression or deficiency in one or the other of the pancreatic ferments.

Undoubtedly, a large number of cases in this group are mild and transitory and will respond to such dietetic measures as make the intestine an ungrateful field for the growth of the organism pathogenic in the particular case.

Schroth Building.

## STATUS THYMOLYMPHATICUS

WITH REPORT OF FOUR CASES IN ONE FAMILY \*

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The condition that forms the subject of this paper can hardly be referred to as a distinct disease entity, yet it presents such a definite clinical picture, with more or less uniform pathologic findings, that it justifies classifying it as a disease state of special clinical significance.

Its nomenclature is influenced to a certain extent by the age in which the condition is observed, and by the predominance of certain clinical and pathologic features, yet as a whole the terms status thymicus, status lymphaticus, lymphatism and status thymolymphaticus are more or less synonymous. The reference further to the instances of mors thymica and thymic asthma are also closely related to this same condition.

Status thymolymphaticus is peculiar to children, but is also observed in the adult, and is characterized by a hyperplasia of the lymphatic tissues and of the thymus in association with a flabby, fat overgrowth of the body, hypoplasia of the heart and blood-vessels, particularly of the aorta, with a lowered constitutional resistance and a tendency to sudden death from trifling causes.

The four children in one family on whom this study is based, were observed by one of us (Goodrich), and presented the following clinical histories:

### CASE HISTORIES

The father of these children is alive and well. The mother died of a heart and lung affection in October, 1910, some eighteen months previous to the death of the first child. In January, 1912, the father again married. In the father's family history there is a record of deaths of eight of his brothers and sisters, all under 9 years of age; three from scarlet fever, one erysipelas, one dysentery, and three from unknown causes. The mother's family history presents nothing of significance.

CASE 1.—April 8, 1912, Wyetta, the second youngest girl in the family, 4 years of age, died suddenly. For a few weeks some impairment of hearing had been noted, and her breathing had been somewhat difficult and stertorous, but this was ascribed to a cold and was treated with home remedies. About a year previously this child passed through an attack of diphtheria, during which she received 5,000 units of anti-diphtheritic serum. While she recovered very well from the diphtheria infection, she had not seemed as bright or active after this time. During a few days before her death this apathy was more marked. She manifested no desire to play and was greatly disturbed by enuresis, both diurnal and nocturnal. About midnight on the night before her death she aroused her father by an attack of choking followed by vomiting, after which she slept

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\* Read in the Section on Diseases of Children of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.



until morning. On arising she was noticed to have a pallid look. She again vomited, was put back to bed, and the physician was summoned, but he found her dead on his arrival.

*Necropsy.*—Examination made by D. J. Glomset, twelve hours after death.

*Record:* Length of body 37 inches. The lips are pale. The abdomen is rather prominent. The cervical, axillary and inguinal glands are enlarged. The limbs are plump. The subcutaneous fat is well preserved. The muscles are pale. The peritoneal cavity is free from adhesions. The pleural cavities are free from fluid and there are no adhesions.

*Thymus:* The thymus is prominent and covers the right auricle completely. It fills the upper part of the anterior mediastinum and lies against the trachea, but there is no evidence of pressure on the windpipe. The organ is made up of two lobes. It measures 5 cm. in length, and 6 cm. in width. It weighs 42 gm.

*Heart:* The pericardial cavity contains a few cubic centimeters of a serous fluid. The right heart is dilated. The orifices are normal. There is a yellowish-gray nodule on the auricular surface of the anterior lip of the mitral valve. This nodule is about the size of a millet seed. The myocardium appears normal.

*Lungs:* The lungs are rather boggy, but crepitate throughout. The peribronchial lymph-nodes are enlarged, grayish-red in color and moderately firm. The largest is about the size of a large bean.

*Alimentary Tract:* Post-mortem changes are present in the stomach mucosa. Six inches above the ileocecal valve the upper part of the bowel has telescoped 2 inches into the lower. There is a hyperemia in the outer part of the bowel, but no signs of exudate or fibrinous adhesions. A large number of the mesenteric lymph-nodes are enlarged, varying in size from that of a pea to a hazelnut. Their consistency is rather firm and their cut surface is grayish in color.

*Spleen:* The spleen is enlarged, lobulated, and moderately firm in consistency. The malpighian corpuscles are prominent, but apparently lessened in number.

*CASE 2.*—Eight days following the death of Wyetta, Louise, a bright and active 2-year-old girl, fell down the cellar steps fracturing her left clavicle. This was reduced soon afterwards by Dr. Goodrich. At this time she seemed bright and sat up in bed while the dressings were applied.

The general physical examination revealed a plump, well nourished child. The abdomen was somewhat prominent, liver and spleen not appreciably enlarged. No rachitic phenomena. The tonsils were large, and the cervical lymph-nodes were enlarged. The thymus was not palpable in the episternal notch, yet the percussion area corresponding to its location showed increased dullness. The following morning at about 7 o'clock she arose, and seemed quite well, eating, however, only a little cake for breakfast. Soon after 8 o'clock she was seized with a spasm, which was soon followed by another. Then she said she was hungry, and was given some strawberries, of which she ate quite heartily. She was then put to bed and was soon asleep. This did not last long, however, for she was shortly heard screaming. By the time her stepmother reached her she was dead.

*Necropsy:* Eight hours after death examination was made by Dr. D. J. Glomset.

*Record:* The body is very pale, a frothy liquid exudes from the mouth, and there are a few ecchymotic spots above the right eye. The cervical and inguinal glands are palpable. A trace of body heat is still present. The abdomen is prominent. Subcutaneous fat is well preserved. The abdominal muscles are pale. The muscles surrounding the left clavicle are infiltrated with blood. The clavicle is broken completely in two, one and one-half inches from the sternal end. The tonsils and adenoids are very much enlarged.

*Thymus:* The thymus is very prominent, covering the base of the heart and filling the upper and middle parts of the anterior mediastinum. It is composed of two lateral lobes and a central lobe, and measures 4.5 cm. in width, by 6.5 cm. in length. It is rather soft, grayish-white in appearance and weighs 54 gm.



**Heart:** The myocardium is soft and flabby. The right heart is dilated. There are two small yellowish nodules just above the aortic valve.

**Lungs and Trachea:** The mucosa of the trachea is congested, but there is no evidence of compression. A frothy fluid exudes from the cut surface of the lungs on pressure.

**Liver:** The liver is soft and has smooth surfaces. There are two yellowish spots present on the left border of the right lobe which extend about one-fourth inch into the substance of the organ.

**Spleen:** The spleen is about normal in size. It is distinctly lobulated and the malpighian corpuscles are strikingly prominent.

**Stomach:** Is moderately distended and contains a semifluid chyme. (This was sent to the chemist for examination, which proved to be negative.) Peyer's patches are prominent and grayish brown in color. The mesenteric glands are enlarged and range in size from that of a pea to a hazelnut. They have a moderately firm consistency.

**Brain:** Substance is very soft. The surface has a damp appearance. No gross pathologic changes.

**CASE 3.**—June 7, 1912, Walter, the only boy in the family, aged 5½ years, died in the same sudden manner as the two other children. Several weeks prior to this time, he, like his sister, Wyetta, was noticed to have some defect in hearing. On account of this, he was brought to the Children's Dispensary service of Dr. Goodrich on May 20, at which time the examination revealed a boy well nourished, sluggish mentally, having a pasty, adenoid appearance, "pot bellied"; the cervical, axillary and inguinal glands were all palpably enlarged. The tonsils were hypertrophied, adenoids were present. The spleen was moderately enlarged. The lungs were normal. The cardiac area was small. The thymus gland was not palpable in the episternal notch, but a distinctly broad area of dulness was demonstrable in the upper part of the sternum.

The urine findings were negative. Several attempts were made to obtain a blood examination, but were constantly opposed because of the fear of the simple prick with the needle that was necessary to secure the sample. A similar objection was made to an x-ray examination, or to the suggestion of its use as a therapeutic agent.

The patient was referred to the service of Dr. Pearson for a laryngoscopic and otoscopic examination, but the report was negative with regard to any abnormal findings. The clinical diagnosis of status lymphaticus was made at this time. A course of syrup of ferrous-iodid was prescribed, and the parents were admonished to watch the boy carefully for any change in his condition.

On the morning of the day of his death he seemed to be in his usual health, and had gone out into the garden amusing himself picking potato bugs off the potato bushes, when he was called inside because it was thought the sun was too hot for him. He went into the house and laid down on the bed, but said he was not sick. Soon after this on going to his room he was found to be dead. One arm had been raised over his head and a little bloody froth escaped from the mouth. His face after death, as in the other two children, had a mottled look.

Earlier in the day, this child had experienced some excitement; his sister had returned from school with her promotion card, this being the last day of school, and he became very much interested, so that he could talk of little else than of what he would do when he entered school in the fall.

**Necropsy:** Made twelve hours post-mortem by Dr. D. J. Glomset.

**Record:** Body plump, pale, and has a goodly amount of subcutaneous fat. The inguinal and axillary glands are palpable on both sides.

**Thymus:** The thymus is enlarged, moderately firm and weighs 25 gm. The tonsils are prominent, as are also the collections of lymphatics at the base of the tongue and in the pharynx. There is no evidence of compression of the trachea.

**Lungs:** There is marked edema of the lungs.

**Lymph-Structures:** The lymphatic structures of the small intestine are prominent. The mesenteric lymph-nodes are enlarged and moderately firm. The spleen is lobulated and the malpighian corpuscles are distinct. The heart is unchanged. The stomach and its contents were sent to Dr. F. J. Smith, professor of chemistry, Drake University Medical School, for examination as to the presence of any inorganic poison, with a negative result.

**CASE 4.**—July 7, 1912, just three months and four days following the death of the first, the last member of a family of four children, Florence, aged 7 years, succumbed to the same affection.

Since the death of the second child and more specially of the boy, Walter, she had been watched very carefully, not only by her family, but by her attending physician as well. She was examined frequently and presented the same physical changes that had been noted in the other children, as hyperplasia of the lingual and pharyngeal tonsillar tissue, the cervical, axillary and inguinal lymph-nodes. There was percussion evidence of an enlarged thymus, prominence of the abdomen, and a moderately enlarged spleen; the child was rather fat and flabby, had a pasty complexion, but seemed to be in good health. A blood and x-ray examination could not be made for the same reasons as in the other cases.

During the last two weeks of her life the "warning deafness" appeared. On two or three occasions in the week preceding her death, she was seized with spells in which she thought she was being choked, but recovered from them rapidly. In one of these seizures she said, "Oh, my God, someone is choking me." She then became cyanotic and sweat profusely; after recovering from it she asked her mother if she had seen all the people about her.

During the night previous to her death she became greatly alarmed because of the thunder storm then raging, but after its cessation she slept quite well. At 7 o'clock in the morning, as her father was going to his work, he awakened her, and as was his custom asked her how she felt; she replied "allright," and returned to sleep. Some two hours later she arose and went to the living room to dress, when it was noted that her head was dropped down on her chest; attempts were made to revive her but without avail and death evidently followed immediately.

**Necropsy:** Made twelve hours post-mortem by Dr. A. S. Begg.

**Record:** Body plump, pale, and has a liberal amount of subcutaneous fat. Abdomen is prominent; skin of thorax is mottled and cyanotic. The inguinal and axillary lymph-nodes are enlarged.

**Thymus:** Enlarged, moderately firm and weighs 40 gm. The dimensions are 4 by 5 centimeters. Marked hyperplasia of tonsils, lymphoid tissue at base of tongue, pharynx, and intestinal tract. Mesenteric nodes are enlarged. Spleen is moderately enlarged. There is some edema of the lungs. Heart is unchanged. No definite pathological change is found to account for death. The possibility of death being due to some chemical poison introduced into the stomach was excluded by a careful chemical analysis of the stomach and its contents after removal from the body.

**Microscopic Examination.**—The microscopic changes found in the lymph-nodes, spleen and thymus in all four of these cases are very similar and are those which occur in any chronic inflammation of the lymphatic system. There was a diffuse proliferation of the endothelial cells in all of the lymphatic structures. In Case 3 there was also an apparent increase of lymphocytes in some of the mesenteric lymph-nodes and in the thymus. In this case, however, the most marked change was an increase of the fixed cells of the lymph-nodes.

In Case 2, which is fairly typical of the others, the malpighian bodies of the spleen were partially replaced by endothelial cells. Only a few germ centers could be found in any lymph-node. There was a distinct increase in the supporting connecting tissue of the spleen and of the largest lymph-nodes. Giant cells were not to be detected.

In the second case there was also a rather marked degree of myocarditis, and in two of the children there was a diffuse atheromatous change in the aorta

of one, and on the mitral valve of the other. Hassall's corpuscles were prominent in all the thymi. There was a homogenous degeneration of the centers of some of the corpuscles of Hassall.

#### SUMMARY OF CLINICAL AND PATHOLOGIC FINDINGS

1. All the cases presented the same symptom-complex: pasty complexion, a flabby fat overgrowth, hypertrophied tonsils and adenoids, enlarged cervical, axillary and inguinal lymph-nodes and signs of an enlarged thymus; all were bottle-fed and had the "pot belly" of the rachitic.

2. Three of the four had a preliminary deafness.

3. Three of the four had seizures of choking or attacks suggesting thymic asthma.

4. All were apparently well nourished.

5. In all no malady sufficient to cause death was noted clinically.

6. In all cases death occurred before the arrival of a physician and under very similar circumstances.

7. No other similar cases are known among the playmates or friends.

8. All were of nervous temperament and became easily excited.

9. One child had diphtheria in 1911 and was given 5,000 units of antitoxin, the other three children receiving at the same time 1,000 units each for prophylactic purposes.

10. The post-mortem findings were practically identical in the four cases: the lymphoid hyperplasia and enlarged thymus prevailed in each. The weight of the thymi were, respectively, 42, 54, 25 and 40 gm.

11. The histologic changes found in all of the cases are extremely suggestive of a chronic inflammation affecting principally the lymphatic tissues. Whether this chronic inflammatory reaction has been produced by poisonous substances formed in some other part of the body or eliminated by some unknown micro-organism affecting the lymphatic tissues, is difficult to say.

12. It is difficult to conceive that the enlargement of the thymus was the main causative factor in the deaths of the children.

#### GENERAL CONSIDERATIONS

All discussions of status thymolymphaticus center about the conception of the pathological physiology of the thymus, and to a lesser degree of the lymphatic apparatus.

Sudden death has been frequently associated with thymic enlargement, the earliest mention of this fact being made by Plater in 1614.

All consideration of congenital and infantile stridor, asthma and sudden death has given to thymic enlargement, whether associated with coincident enlargement of the lymph-node or not, a clinical interest of considerable importance, about which an interesting controversy has been waged for a long time.



Paltauf<sup>1</sup> increased our knowledge of the subject when he described in 1889 a lymphatic constitution: he associated with status lymphaticus a hyperplasia of the heart and arterial system, and ascribed to it the condition of lowered resistance and increased tendency to fatalities in the various acute infections.

In a recent contribution on the pathology of the thymus by Wiesel<sup>2</sup> and the clinical discussion of status lymphaticus as exhaustively considered by H. Matti,<sup>3</sup> a most comprehensive view of the subject is obtained.

The anatomical status of the thymus cannot be said to be definitely fixed. Originally an epithelial structure, these elements gradually undergo various retrograde changes, but the epithelial remnants persist in the connective corpuscles of Hassall. At birth the lymphoid character of the organ is so marked that it is usually classed with the lymph-nodes. Some class it with the ductless glands; others place it without question among the lymphoid organs.

In many ways the thymus may be regarded as a homologue of the tonsils.

The estimation of thymus enlargement is subject to more or less error. Dudgeon<sup>4</sup> places the average weight of the thymus at from 7 to 10 gm. from birth to 2 years of age; Hart,<sup>5</sup> Friedleben<sup>6</sup> and Rolleston<sup>7</sup> also conclude that the acme of growth is reached by the end of the second year, then undergoes retrograde change, yet may remain stationary until puberty, which is followed by rapid physiological involution.

Glands weighing 20 to 30 gm. must be considered as enlarged.

The following tables of weights as collected by three different observers represent the variations peculiar to statistical studies:

Hammer <sup>8</sup>		Friedleben <sup>6</sup>		Von Sury <sup>9</sup>	
Age	Wt. Gm.	Age	Wt. Gm.	Age	Wt. Gm.
New-born	13.26	1 yr. 9 mo.	20.7	New-born	14.4
1-5	22.98	9-24	27.3	1 mo.	15.
6-10	26.10	2-14	27.	2-9	24.3
11-15	37.50	14-25	22.1	9 mo. 2 yr.	23.3
16-20	25.58	25-33	3.1	2-14 yr.	25.
21-25	24.73	.....	.....	.....	.....
26-35	19.87	.....	.....	.....	.....
36-45	16.27	.....	.....	.....	.....
46-55	12.84	.....	.....	.....	.....
56-65	16.	.....	.....	.....	.....
66-75	6.	.....	.....	.....	.....

1. Paltauf: Wien. klin. Wchnschr., 1889, ii, 877; 1890, iii, 172.

2. Wiesel: Pathologie der Thymus. Ergebn. v. Lubarsch-Ostertag 15 Jahrg., 1911, Suppl. 2, p. 416.

3. Matti: Ergebn. d. inn. Med. u. Kinderh., 1913, x.

4. Dudgeon: Jour. Path. and Bact., 1905, x, 173.

5. Hart: Grenzgeb. d. Med. u. Chir., 1909, 0, 321.

6. Friedleben: Physiologie d. Thymusdruse. Frankfurt, 1858.

7. Rolleston: Clin. Jour., 1898, xiii.

8. Hammer: Arch. f. Anat. u. Physiol. Anat., Suppl., 1906.

9. Von Sury: Vrtljschr. f. gerichtl. Med., 1908, xxxvi, 88, Series 3.



Hammer's weights are regarded as too high, and were mostly compiled from cases of accidental deaths. Lubarsch<sup>10</sup> claims that status thymicus is very rare in the new-born and young children.

Status thymico-lymphaticus is more frequently observed in older children and adults, thus strongly suggesting that it is an acquired post-natal condition.

The primary cause of thymic enlargement may be sought in any infection, intoxication or disturbance of metabolism, in which there is a



Fig. 1.—Photographs of the four children taken in October, 1911.

lymphoid or myeloid exhaustion. Sahli considers it a criterion of nutrition in infants, associating it with apparently well-nourished pasty children.

The enlargement of the thymus may be regarded, therefore, as a secondary process of the nature of a compensation.

10. Lubarsch: Jahreskurse f. Arztl. Fortb., 1912, p. 56.

It may be associated with or without lymphatic enlargement. In the same light we are reminded of the observation of Kolisko<sup>11</sup> that the mesenteric glands and lymphoid tissues of the intestinal tract are often so prominently enlarged in enteritis of children as to completely obscure the primary inflammatory process.

In the anatomic findings of the four cases included in this paper, there is revealed principally a lymphoid and fibrous tissue hyperplasia that is very suggestive of a reactive process to some form of irritation.

The familial tendency peculiar to our cases has been noted by a number of other observers, Hennig,<sup>12</sup> Friedjung,<sup>13</sup> Perrin,<sup>14</sup> Hedinger,<sup>15</sup> Griffith<sup>16</sup> et al. Hedinger reports an instance in which five members of a family of nine children died suddenly, one of which came to autopsy with the usual findings of status lymphaticus.

Perrin reports in a family of eleven, nine children, and Griffith seven children in one family, from 1 to 8 months of age, who died suddenly with symptoms of dyspnea and cyanosis.

There is no record in the literature of any definite hereditary transmission of this condition.

Our knowledge of the physiology of the thymus is largely based on the experimental work that has been done, principally as the result of thymectomies in animals. The most extensive work is that of Klose and Vogt<sup>17</sup> and H. Matti,<sup>18</sup> from which the following facts are obtained,

Thymectomized dogs present several distinct stages:

1. A latent period of two to four weeks, during which there is no appreciable change.

2. A stadium adipositas continuing two to three months.

3. A stadium cachecticum of three to four months' duration.

4. Death usually within a year.

In addition, a marked change is noted in the general condition, the nutrition is retarded, growth is arrested and bony changes occur very similar to those of rachitis.

There is evidently a distinct connection between thymectomy and the process of ossification.

The removal of the thymus has a depressing influence on the sexual apparatus. A hyperplasia of the thyroid gradually occurs and also some hyperplastic change of the adrenals, hypophysis and pancreas.

11. Kolisko: *Handb. d. Aerztl. Sachverst. Tätigkeit*, 1906, ii, 701.

12. Hennig: *Gerhard's Handb. d. Kinderkrankh.*, 1893.

13. Friedjung: *Grenzgeb. d. Med. u. Chir.*, 1900, iii, 465.

14. Perrin: *Ann. de méd. et chir. inf.*, 1903, vii, 217.

15. Hedinger: *Deutsch. Arch. f. klin. Med.*, 1905, lxxxvi.

16. Griffith: *New York Med. Jour.*, 1909, xc, 444.

17. Klose and Vogt: *Beitr. z. klin. Chir.*, 1910, lxxix.

18. Matti: *Grenzgeb. d. Med. u. Chir.*, 1912, xxiv, 665.



Fig. 2.—The two older children (Cases 3 and 4). Photograph taken in April, 1912.

In the injection of thymus extract, Svchla<sup>19</sup> has demonstrated a pressor substance. Vincent<sup>20</sup> and Popper<sup>21</sup> report similar results, while Oliver and Schafer<sup>22</sup> and Morehead obtained negative results.

Thymus feeding has not led to any definite results, and the third attempt to produce a state of hyperthymization by means of thymus transplantation, carried out mainly by Sommer and Florken<sup>23</sup> and Ranzi and Tandler,<sup>24</sup> has also not given any reliable or uniform results.

From the experimental results reported, it is evident that dethymization is attended by rather definite systemic disturbances, particularly in the process of ossification and growth of bone, but the opposite state of hyperthymization is by no means as clearly defined.

The apparent association with the chromaffin system is evident, and in the opposing as well as controlling influence of thymus extract on the secretion of the other ductless glands, there is strong suggestion of a separate internal secretion of the thymus, yet it still lacks much corroborative evidence.

In connection with the hyperplastic changes in the thymus and the lymphatic apparatus, some interesting findings have been observed in other organs.

Wiesel refers to the presence of thyroid enlargement in status thymicus. The association of Basedow's disease with status thymolymphaticus has been demonstrated in a large number of instances by Capelle.<sup>25</sup>

The larynx is often small and of the heterosexual type.

The hypoplasia of the aorta, as well as its branches, and the small heart have been referred to. Von Neusser<sup>26</sup> has called attention to abnormal length of the bowel and atypical lobulation of the lungs. Shiota<sup>27</sup> has reported the occurrence of an abnormally long appendix vermiformis. Wiesel<sup>28</sup> has found hypoplastic adrenals in well-marked examples of this condition, and the interesting contribution of Hedinger<sup>29</sup> corroborates the coincidence of Addison's disease with status thymolymphaticus.

In a careful study of fifteen cases of Addison's disease he found eight instances of status lymphaticus, four cases of status thymolymphaticus

19. Svchla: *Arch. f. exper. Path. u. Pharm.*, 1900, xliii, 321.

20. Vincent: *Arch. Physiol.*, 1904, xxx, 16.

21. Popper: *Sitzungsber. f. Acad. d. Wissensch. Wien.*, 1905, cxiv, 539.

22. Oliver and Schafer: Cited by Matti, *Ergebn d. inn. Med. u. Kinderh.*, 1913, x; Morehead: *The Practitioner*, 1905, lxxv, 733.

23. Sommer and Florken: *Sitzungsber. d. physiol. med. Gesellsch. Würzburg*, 1908, 3 suppl., p. 15.

24. Ranzi and Tandler: *Wien. klin. Wchnschr.*, 1909, xxii, 980.

25. Capelle: *München. med. Wchnschr.*, 1908, p. 1826.

26. Von Neusser: *Zur Diagnose der Status thymico-lymphaticus*, Wien, 1911.

27. Shiota cited by Matti: *Ergebn d. inn. Med. u. Kinderh.*, 1913, x.

28. Wiesel: *Virchows Arch. f. path. Anat.*, 1904, clxxvi, 103.

29. Hedinger: *Frankfurter Ztschr. f. Path.*, 1907, i.



and three cases incomplete. These observations have been corroborated by Warthin,<sup>30</sup> Pappenheimer<sup>31</sup> and others. Bartel<sup>32</sup> has associated glioma of the brain with the condition under discussion. Marie<sup>33</sup> found acromegaly with status thymicus. Von Recklinghausen reported the presence of status thymolymphaticus in a case of osteomalacia.

The association of a lymphatic constitution with rickets has been frequently emphasized.

The sudden death in status thymolymphaticus, which forms such a tragic chapter in this condition, has been variously explained, and continues to be a problem of considerable controversy and discussion.

The several theories that have been proposed may be grouped as follows:

1. Mechanical: pressure of enlarged thymus on the trachea or contiguous blood-vessels, causing stridor, asthma and death.
2. Intoxication due to faulty tissue changes similar to the action of syphilis on the heart muscle (Paltauf).
3. Hyperthymization resulting from pathological increase of an internal secretion, both of the thymus and of the lymph-nodes.

Paltauf's explanation has been largely discarded in view of the lack of any supporting evidence.

The mechanical theory is also not sufficient, as so many of the cases show no previous signs of thymic asthma.

Until the existence of an internal secretion has been more definitely demonstrated, it will not be consistent to attribute thymic death to a state of hyperthymization. On the other hand, a critical review of the literature, giving due consideration to all anatomic relations, a mechanical thymus death by tracheal compression, in rare instances also by compression of the blood-vessels, is a distinct possibility, and in a number of instances has been definitely proved to be the cause of death.

Birchner<sup>34</sup> has demonstrated by experimental means the toxic effects of injections with pathologic thymi.

In adults a cardiac death is the rule, and it seems proper to refer to a "thymic heart" in the same sense that the term thyroid heart is used.

Again, it is not so much the thymic hyperplasia as the coincident unfavorable factors that attend this state, which are probably largely to blame for the fatal outcome. The death is often induced by a number of influences that have no effect on the normal individual.

30. Warthin: *Arch. Pediat.*, 26, 1909, xxvi, 597.

31. Pappenheimer: *Jour. Med. Research.*, 1910, xxii.

32. Bartel: *Wien. klin. Wochenschr.*, 1908, 783.

33. Marie: *Gaz. d. hôp.*, 1893, lxxvi, 202.

34. Birchner: *Centralbl. f. Chir.*, 1912, No. 5, p. 138.

## DIAGNOSIS

The recognition of status thymolympathicus should present no difficulty, since the associated symptom-complex is usually so well defined. Unfortunately, in the past the attention was not directed toward these unfortunate patients until after a sudden death had occurred.

It should be possible to detect complete as well as incomplete types before the fatal exitus manifests itself.

## TREATMENT

This resolves itself into prophylactic and curative. Under the former should be emphasized:

1. Avoidance of excitement.
2. No surgical operation unless absolutely necessary, as these patients do not take any kind of anesthetic well.
3. Very warm or very cold baths are to be avoided, as the shock has been known to cause death. Cases of sudden death while swimming may be ascribed to this cause.
4. Prevention of infection, especially of the upper respiratory tract.
5. Securing good hygienic conditions of life.

As regards the curative treatment of status thymolympathicus, it can hardly be considered as curative in its true sense, since it is more of an attempt to treat and relieve certain symptomatic manifestations of the condition. A medicinal or internal form of treatment is not applicable at all. Of the non-medical therapeutic measures, mention should be made of the following:

1. Intubation with a long tube reaching to the bifurcation of the trachea, being of special value in cases of thymic pressure.
2. Thymectomy, partial or complete, is an operation of considerable surgical risk, yet carried out successfully by Rehn,<sup>35</sup> Veau and Olivier,<sup>36</sup> and more recently by Jackson<sup>37</sup> in this country.

This operation has for its purpose the relief of thymic pressure and removal from the system of the toxic influence of a pathological thymus.

3. Radiation. The use of the Roentgen ray has been espoused by Friedlander,<sup>38</sup> Heinecke<sup>39</sup> and Regaud and Cremieu,<sup>40</sup> and all report brilliant results in producing involution changes in the enlarged thymus. This agent will be equally effective in reducing the size of the spleen and the hyperplastic lymph-nodes.

Because of greater safety and evident efficacy its use is to be recommended.

35. Rehn: *Arch. f. Klin. Chir.*, 1906, lxxv, 468.

36. Veau and Olivier: *Jour. de méd.*, March 15, 1912.

37. Jackson: *Jour. Am. Med. Assn.*, 1907, xlviii, 1753.

38. Friedlander: *Arch. Pediat.*, 1911, xxviii, 810. No. 10.

39. Heinecke: *Grenzgebiete d. Med. u. Chir.*, 1905, xiv, 24.

40. Regaud et Cremieu: *Thèse de Lyon*, 1911.

## NEEDLE IN THE HEART FIFTEEN MONTHS; DEATH, AUTOPSY \*

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NEW YORK

*CASE: R. Z., aged 2  $1\frac{1}{2}$  years, under observation at the Presbyterian Hospital, N. Y.; accident when 1 year old; died; autopsy.*

A puny, undersized child was brought to the out-patient department of the University and Bellevue Hospital Medical College, the parents hoping that she might be strengthened, her color improved, her bronchitis cured. She was announced to me among the material for clinic as "congenital heart disease." She was not cyanotic. I put my hand over her chest and felt the purring thrill. I presumed it to be a case of congenital heart in which there was no cyanosis, an exception to the rule. On further examination it was noticed that the murmur, though loud and purring, was heard all over the chest, and was not of maximum intensity over the left space and costo-sternal junction. The maximum was rather over the belly of the left ventricle. The physical signs were exceptional and not at all convincing; but since the child was so young and had no previous history of illness, it was presumed that it must be really a case of congenital malformation without cyanosis. The unclassical points here mentioned led me to make an effort to get the child into hospital for further observation. When it arrived at the Presbyterian Hospital I went through the same preamble to the staff. After two examinations I asked for a radiograph, to learn the size of the right ventricle and for any chance information that might be gained. The accompanying illustrations show what the x-ray revealed (Fig. 1). One plate exposure caught the heart just in contraction and gave two parallel shadows. Two right-angle exposures located the foreign body in the cavity of the left ventricle.

Amusing stories are told of the weird effect that the first developed plate had on the photographer. It is said that he believed the plate had a defect in it; that in the second plate the camera was defective; in the fourth and fifth and subsequent plates that his brain was touched. I cannot vouch for these stories.

Now that the diagnosis was made, the question arose, How was the needle to be removed? While the surgeons were discussing the matter the child developed bronchitis. She recovered from this, and after

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\* Read before the American Pediatric Society, Washington, D. C., May 7, 1913.

remaining in the hospital for a month or more, it was thought best to remove her to the country. There was no hope for the removal of the needle and really no hope of the child's living in her present condition. After a short sojourn in the country the child returned suddenly to the hospital with pneumonia, and died within twenty-four hours and consequently was a coroner's case.

The coroner made a most careful and thorough autopsy, and I am able to give a completed history. The needle was found as predicted, free in the left ventricle, butt-end down (Fig. 2). The needle was slightly corroded. There was no ante mortem clot and no inflammatory action about it. It pierced and extended beyond the mitral valve and scratched the endocardium of the auricle. In the auricle there was an area of superficial ulceration where the point of the needle had rubbed off the endothelium. The apex of the heart was adherent to the pericardium about the region through which the needle went, for an area the size of a quarter of a dollar. There was also a little roughening of the pericardium about the adherent area. This was the sum total of the irritation which the needle gave in its travel through the diaphragm and pericardium. On the under-side of the diaphragm was a streak of rust or dark staining (Fig. 3), showing the course by which the needle had traveled from the abdominal cavity to the ventricle.

The needle entered the abdominal cavity by way of the skin surface, presumably at the time of the fall at the age of 1 year. By one thrust it was shoved into the very apex of the heart, the butt-end of the needle remaining just within the skin of the abdominal wall, the point possibly extending even into the cavity of the ventricle. The point of entrance into the skin was at the most exactly near point, viz., at the left side of the ensiform cartilage close up to the ribs; likewise, the exact point of entrance into the apex was at the septum. The direction of the needle was such as to miss the right ventricle and proceed straight to its resting place in the left heart. There was no evidence that the needle had touched the liver or done injury to any other abdominal tissues or organs. After the first thrust, it is easy to know its mode of advance. Every muscular contraction sent it forward on its way, point foremost, till it lay free in the cavity of the heart. The butt-end was free in the cavity's apex, and since the needle was longer than the cavity, the point extended up into the auricle, as mentioned above, thrust through the one leaf of the mitral valve.

There is but little authentic history, but this is a summary of what the parents gave. The child was, on entrance, 2 years old. When 1 year old, it fell out of a wooden cradle. At that time the mother noticed a protrusion just below the ensiform cartilage in the mid-line, "like a nail," "as if the child had swallowed something," but the mother knew



nothing of anything swallowed. She said that she took her to a doctor who felt the swelling, but said it would go down, and so it did. There was no abrasion of the skin anywhere. The fall gave no severe results at the time, though the mother says that since that time the child has gradually failed. In one conversation there are stray remarks that the swelling did not come till two weeks after the fall; that there was pain; that she took her child to the doctor for pain, and that there was stomach

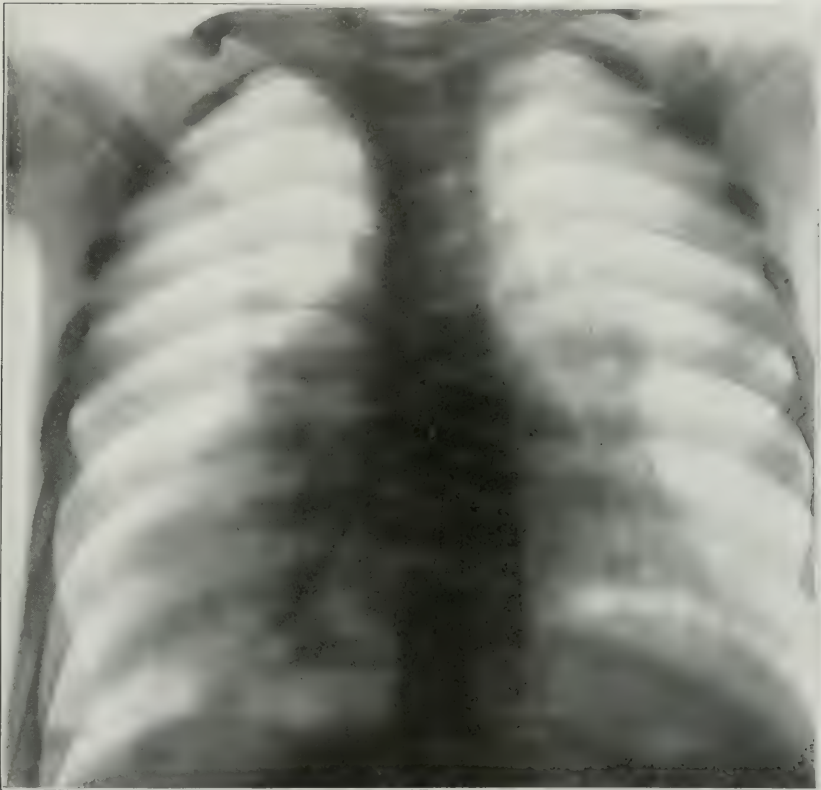


Fig. 1.—Needle fifteen months in the left ventricle of a child 2½ years old.

trouble. One cannot doubt that there may have been pain and gastric disturbance, but in that class of observers exact details are not forthcoming. It may be believed that there was protrusion ("swelling") in the epigastrium; that there was "fever," considerable "heaviness of the chest"—dyspnea, especially at night.

The hospital historian recapitulates as follows: Chief complaints, heaviness of the chest, at night; paleness; diagnosis, congenital heart lesion.

Twelve days after the child was sent to the country to build up its strength and blood, it returned with symptoms of pneumonia, and the same day it died. An autopsy was made. The photographs show the needle in position.

While this case was the absorbing topic of conversation, a patient waiting in the hall heard something said which stimulated the father to offer a remark of interest in this connection. "Why, my baby had a

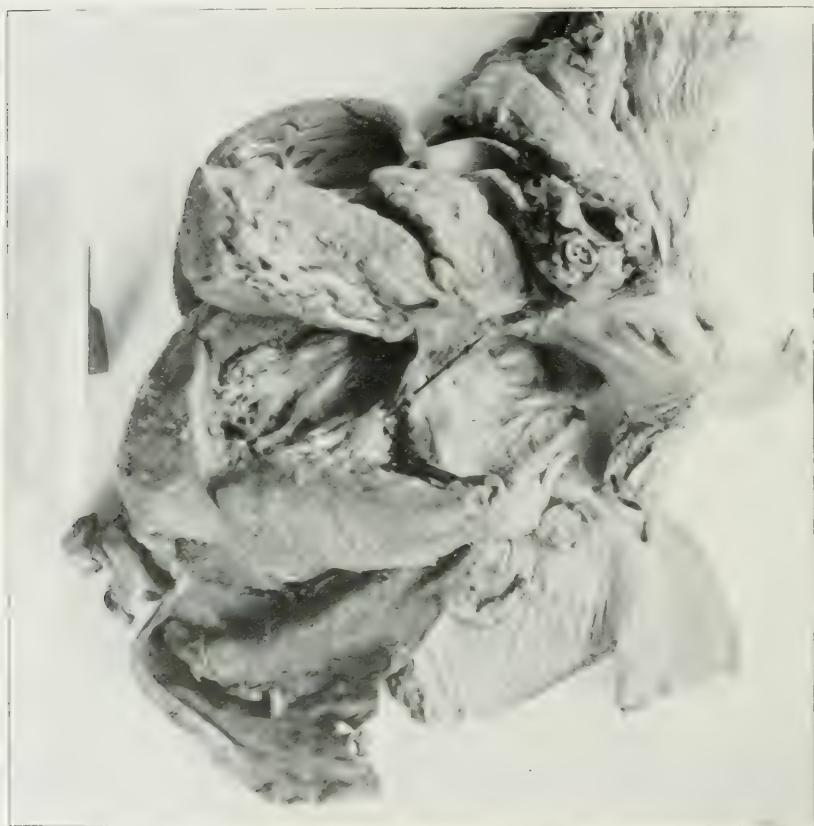


Fig. 2.—Needle in the left ventricle; point stuck through the mitral valve; butt-end is within the cavity of the ventricle.

needle in her belly," he volunteered. "The nursemaid had a needle and thread stuck in the shoulder of her dress. She was dandling the baby up and down on her shoulder," peering, no doubt, far out the window to see the nearest policeman on the beat. "All at once the needle was gone, the child failed to be quieted by the dandling on the shoulder, and when it came time to put the child to bed there was noticed to be hanging out of the belly a thread. On pulling at the thread, out came a little more

thread and finally a needle. This conversation was volunteered, was repeated verbatim by each of the parents separately, and not in each other's presence. We purposely made little of the incident, and when they were not in the sight and hearing of each other, we asked them about it as though it were not of the least importance, and the father and mother repeated the same story in the same words. Both had been present at the extraction of the needle and thread, and both told the same story.

However the needle in the case here reported started on its way, there is no mystery as to its method of progression. Like all needles in

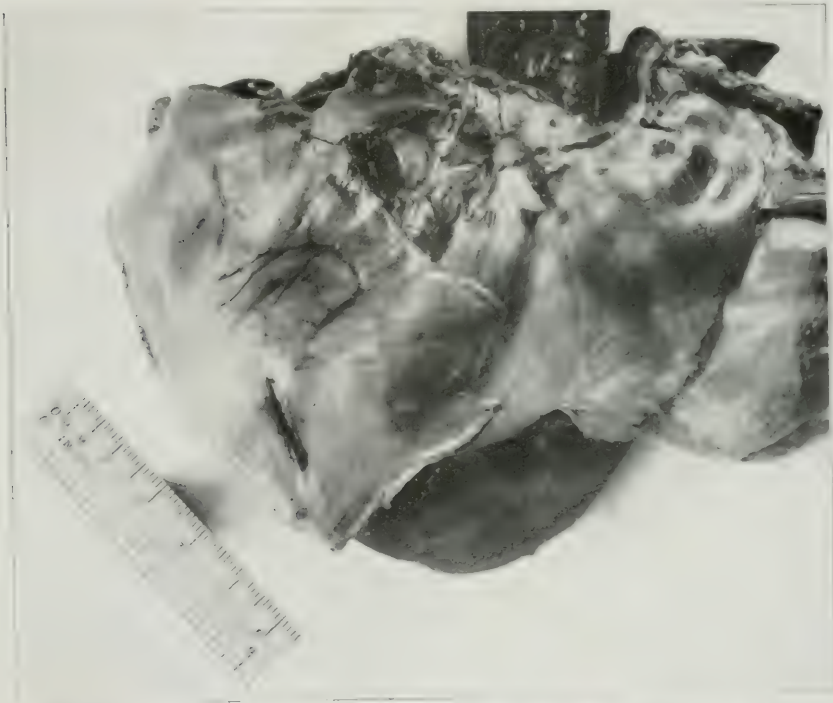


Fig. 3.—Needle in the left ventricle. Dark line near the measure is the suture showing the track through the diaphragm.

the tissues, it progressed point first, each step being in time with some muscular contraction.

How the needle came to be in position to pass by one clean thrust from the outside world quite out of sight within the integument, is of course entirely conjectural. A nurse has suggested that some people prefer to sew the garments on rather than use safety pins. In such a case it is quite within the range of possibility that a needle was left in the diaper ready to be thrust forward as the child fell over the crib.

It is of little value to discuss the physical signs of this unusual lesion. However, the murmurs were of nearly every variety. Over the belly of the ventricle the murmur was double; at the apex it was loud systolic; at the base it was also systolic and loud. The heart was large.

The condition of the needle was also of interest. One might suppose that the needle would be much corroded and that an ante mortem clot would be found. On the contrary, there was but little corrosion. As seen in the picture, there were little beads along the shaft, but not much. There was no sign of clotting before death.

The needle was the ordinary one used in sewing coarse garments, or, more properly, undergarments. It was about two inches long. It traveled by the shortest route possible from the outer world to the ventricle. It seemingly entered at the side of the ensiform cartilage, went straight to the apex and so on to its place in the ventricle.

It is useless to discuss the possibility of its removal during life, and yet it was a fascinating ground for speculation at the time. A powerful electro-magnet was suggested by more than one. There was no hope for the child without surgical interference, and the needle had been in place for more than a year. It was also quite true, as the mother said, that the child was remaining stationary or losing ground in spite of the best of care. In short, there was little or nothing to lose by operation, and possibly something to gain. However, there was no operation, and in the light of the autopsy findings, it is fortunate that there was none. The parents, I might say, were quite willing to have anything done that the surgeons could recommend. In fact, they threatened to take the child out and possibly try elsewhere if something was not done, which, being interpreted, meant an operation.

The child was in the hospital three months, became quite content with her surroundings, and yet she had these peculiarities to the very end. She never spoke a word to any one of the staff for two months, did not smile in that time, yet was quiet, sat up in bed and after the first few examinations and visitations, never cried. She was a weird little thing, sitting in her crib looking straight forward into the eyes of all callers, as though she but faintly saw them.

57 East Seventy-Ninth Street.



## THE DIAGNOSIS OF INTUSSUSCEPTION BY X-RAY

IRVING M. SNOW, M.D., AND MARSHALL CLINTON, M.D.

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The following case presents so many points of interest that it is herewith reported:

*History.*—The patient was the third child of healthy parents, born after a normal labor. She was nursed, but the mother suffered from sore nipples so much that she cried each time the child was put to the breast. When the child was 5 weeks old it vomited a clear bloody fluid and some hours afterward passed a black, tarry stool, but showed no other evidence of illness. It was supposed that the infant had swallowed blood from a fissured nipple, but the mother immediately withdrew some clean milk with a breast pump, and it is possible that the symptoms were due to a slight intussusception which was spontaneously released.

For the next few weeks the baby was fed from the breast, but the milk began to diminish and it was given supplementary feedings of cow's milk and a malted food.

November 6. The child was now 3 months old; it took the bottle well at 3 a. m., and afterward slept. At 6 a. m., it refused the breast and seemed quite ill. The child commenced to cry with pain, vomit and pass frequent stools of mucus and blood. The fifth vomiting attack showed regurgitation from the small intestine.

*Examination.*—At 8 a. m., a rectal examination was made with negative results. Directly after the withdrawal of the finger a quantity of fresh blood flowed from the anus. The abdomen was relaxed and on palpation a sausage-shaped tumor, moveable and insensitive, was felt in the left upper abdominal quadrant. The temperature was normal, the heart strong and regular. No medicine was given and feeding was stopped.

*Diagnosis.*—Dr. Edgar McGuire saw the infant in consultation at 10 a. m., and considering the positive symptoms present, colic, vomiting, bloody stools and a tumor in the upper abdomen, agreed with the writer (Snow) that the child was suffering from intussusception. As Dr. Marshall Clinton had been selected to operate, to relieve the child, a warm, normal salt solution was injected under pressure into the rectum.

Following this the child became easy and comfortable and slept. The vomiting stopped and the bloody mucous stools ceased, and when Dr. Clinton examined the patient at noon it was impossible to outline the abdominal tumor. This disappearance of the tumor is explained by the

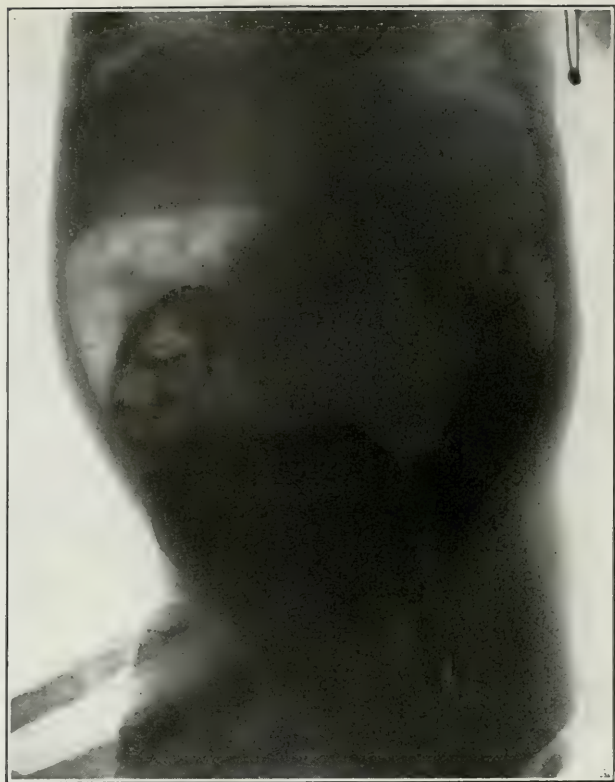


Fig. 1.—Bismuth filling large intestine up to beginning of the intussusception; small amount of bismuth in dilated small intestine above constriction.



Fig. 2.—Bismuth forced under pressure alongside intussusception, filling large intestine up to ileocecal valve.



Fig. 3.—Dr. Parmenter's case of intussusception. Plate taken as soon after injection as possible, showing the obstruction at the splenic flexure.



Fig. 4.—Plate taken about three minutes after plate in Fig. 3, showing some of the bismuth forcing its way beyond the splenic flexure.



Fig. 5.—Plate made five minutes after plate in Fig. 4, and ten minutes after the injection, showing bismuth passing into the large intestine around the intussusception.



Fig. 6.—Plate made ten minutes after plate in Fig. 5 showing still more bismuth passing through.



progressive shortening of the mesentery which pulled the mass of gut to the post-part of the abdomen.

It was, nevertheless, decided that the intussusception was not reduced and suggestion was made that a radiograph be made with the colon filled with bismuth emulsion.

At 4 o'clock the child was taken to the office of Dr. Leonard Reu, where two pictures were taken, after injecting the colon with bismuth and acacia mixture; an additional amount of bismuth was injected between the first and second exposures.

The patient did not suffer from this manipulation and was taken home apparently undisturbed.

The radiograph showed an unreduced intussusception in the right upper quadrant of the abdomen. A small amount of bismuth emulsion had been forced through the gut above the point of constriction.

Late in the afternoon the temperature was 101 F., pulse 150, and the baby passed a bloody mucous stool.

At 7 p. m. the child was taken to the Buffalo General Hospital, where an operation was performed by Dr. Clinton.

*Operation.*—After iodine preparation of the abdomen and the administering of a minute hypodermic of morphin, under ether anesthesia, the abdomen was opened in the median line just above the umbilicus for  $1\frac{1}{2}$  inch. The abdominal wall was infiltrated with a 1 per cent. solution of novocain and then a 1 per cent. solution of quinin and urea hydrochlorid.

The intussusception was located by touch, and with two fingers the intussusception was squeezed out, with no attempt to bring it outside the wound. The invagination was ileocecal,  $\frac{3}{4}$  inch of ileum being jammed into the cecum and colon.

After reduction, which was easily performed, the ileocecal junction was brought into the wound and three mattress sutures were placed in the sides of the ileum and the wall to try to prevent a recurrence. A further infiltration of the peritoneum with urea solution was made before closing the wound, which was sewed up in layers in the usual way. Time of operation, twenty minutes. Time of operation after the onset of symptoms, thirteen hours.

*After-Course.*—After the operation the child was taken home and 2 drops of paregoric and 2 teaspoonfuls of water were given per rectum every hour during the night.

Next morning the baby passed flatus freely and considerable bismuth mixture. Temperature, 100.4; heart rapid but strong. Child comfortable and had lost but one-half pound in weight.

There was a rapid convalescence, but as the mother's milk failed, and as cow's milk disagreed, it received and thrived on condensed milk. At 7 months of age, 4 months later, the weight was 20 pounds.

The case was observed practically from the time the invagination occurred until operative relief thirteen hours later.

After giving a saline injection a deceptive amelioration occurred. All symptoms disappeared and the condition was masked for several hours until a radiograph was made.

An additional case of intussusception diagnosed by x-ray is reported by Dr. J. Fred Parmenter as follows:

*History.*—G. B., aged 9 months, entered the Children's Hospital May 7, 1913, suffering from facial lupus vulgaris and malnutrition. Family and past history negative.

*Present Illness.*—June 17, 1913, after passing a good night and seeming in perfect health, the infant took food at 8 a. m. and had a large, yellow, normal stool at 9 a. m. At 10 a. m. the child suddenly vomited a large quantity of food and began to look quite ill. At noon, during rounds, a nurse called attention to the child, from whom she had just removed a bloody diaper. Abdominal examination showed a rather tender mass on the left side just below the umbilicus. Diagnosis of intussusception, and immediate operation advised, which was accepted by the parents.

*Radiographic Diagnosis.*—At Dr. Snow's suggestion radiographs of the colon were made at 1:30 p. m. by Dr. Leonard Reu, the bismuth solution being introduced per rectum, which verified the clinical diagnosis, as the accompanying plates will show, Dr. Reu's interpretation being as follows: Plate (Fig. 3) taken as soon after the injection as possible, one to two minutes, shows the obstruction at the splenic flexure. Plate (Fig. 4) taken about three minutes later shows some of the bismuth forcing its way beyond the splenic flexure. Plate (Fig. 5), five minutes after No. 2, and about ten minutes after the injection, shows more bismuth passing into the large bowel around the intussusception, while Plate (Fig. 6), taken ten minutes later, shows still more bismuth passing through. Patient's condition immediately improved after the injection, this being due to the slight temporary relief of the obstruction, which was producing shock. The patient vomited and had several bloody stools before the operation, which was performed by Dr. Parmenter, assisted by Dr. Joseph Lewis, at 3:30 p. m.

*Operation.*—Ether anesthesia. Iodin preparation, high median incision; intussusception found on left side, just below the splenic flexure, was delivered and reduced by gentle taxis and pressure on the colon side as suggested by Moynihan. The cecum and ascending colon were practically devoid of mesentery, which accounted for finding the tumor so early on the left side. It was deemed advisable to remove the appendix, which was done, and the abdomen was closed in the usual manner. The intussusception began at the ileocecal valve, and several inches of ileum were telescoped into the colon as far as the splenic flexure. Duration of operation eighteen minutes; uneventful recovery, to date, ten days.

The case is reported because of the opportunity afforded of making an early diagnosis and the unusual location. The intussusception was immediately diagnosed and operated on six hours after commencement of symptoms.

Inasmuch as the life of a patient with intussusception depends on an early diagnosis, and as the clinical picture may be atypical, with some important symptoms lacking, as abdominal tumor or intestinal hemorrhage, the aid of the x-ray in the diagnosis of suspected intussusception should come into common use.

As far as we are aware, ours is the first reported case in which a radiograph was taken to confirm the diagnosis of an intussusception.

476 Franklin Street.

MUCOUS CYST OF THE CECUM IN AN INFANT TEN WEEKS  
OLD, PRODUCING OBSTRUCTION OF THE ILEO-  
CECAL VALVE AND SYMPTOMS SIMU-  
LATING AN INTUSSUSCEPTION \*

A. D. BLACKADER, M.D.  
MONTREAL

For the privilege of reporting this very interesting case I am indebted to the courtesy of my confrères in the Montreal General Hospital, Drs. J. M. Elder and A. H. Gordon.

*History.*—Chas. H., aged 10 weeks, was first seen in consultation by Dr. Gordon March 9, 1913, for continued vomiting. The infant had been nursed by its mother and had thriven well for the first two months of life. Then it began to vomit after taking nourishment. The physician who first saw it regarded the mother's milk as the cause of the trouble and advised artificial feeding. This was tried without benefit; the vomiting persisted and the nutrition failed rapidly. There was no pyrexia. When Dr. Gordon saw it in consultation he recognized a sausage-shaped tumor in the left lower right quadrant of the abdomen and recommended immediate operation. It was at once brought to the Montreal General Hospital and placed under the surgical service of Dr. Elder.

*Examination.*—The notes on entrance are as follows "Infant, 10 weeks old, well developed for age; nutrition poor; very little subcutaneous tissue; no glandular enlargements; lungs and heart normal; abdomen distended. In the right lower quadrant is a sausage-shaped tumor, distinctly palpable, 3 inches long by about 1 inch in diameter, freely movable, not tender; no muscular rigidity of abdominal walls. Distinct peristaltic waves are noticed traveling toward the site of tumor. Temperature 99, pulse 140, respirations 40."

*Treatment and Course.*—Shortly after entrance into the ward a high enema was given which brought away no flatus, and only a small amount of feces, in which there was no appearance of blood or much mucus. Following this the abdomen was immediately opened by Dr. Elder under spinal anesthesia. The oblong tumor mass was found to involve the lower portion of the ileum and cecum; above the mass the ileum was much distended, while below it the ascending colon was collapsed. Regarding it at first as an ileocecal intussusception, careful efforts were made at reduction, and when they failed, a resection was performed with end to end anastomosis, and the abdomen closed. On examination afterward of the incised mass its true nature was disclosed.

The child had no symptoms of shock after operation and for several days its condition was good. On the third day the temperature fell to normal, the abdomen was soft, the bowels moved freely and the infant was placed under my charge for its feeding. On the tenth day after the operation, however, the pulse became weaker, the face assumed an earthy hue, the features became drawn, and on the morning of March 24, twelve days after the operation, death occurred from peritonitis.

\* Read at the meeting of the American Pediatric Society, Washington. D. C., May, 1913.

\*Submitted for publication June 22, 1913.



*Pathologist's Report.*—The pathological report on the specimens removed at operation was as follows: "The tumor consists of the lower portion of the cecum with its contained cyst, and the appendix. The cyst, much collapsed, measures about 2 cm. in diameter, is unilocular, contains glairy mucoid material and is situated on the wall of the cecum opposite the ileocecal valve, extending over to and completely obstructing that orifice."

*Microscopical Examination.*—Microscopic examination of the cyst walls showed the surface of the tumor projecting into the lumen of the cecum to be covered with mucous membrane similar to that of the intestine; the cyst to be lined with a somewhat stretched layer of columnar epithelium which, however, in some places was folded into gland formations. Beneath each surface of epithelium was a submucosa infiltrated with lymphocytes, and between these again are three more or less distinct layers of muscle.

*Diagnosis.*—From this report the cyst was regarded as in all probability a retention cyst, arising either from some fault in development or from an inflammatory occlusion of the mouth of the original gland.

Retention cysts of the appendix are not very uncommon and many cases have been reported during the past few years by various writers, but after a careful search of the literature I have been able to find no instance of a retention cyst of the cecum exactly similar to the one I am reporting. Harrington Sainsbury,<sup>1</sup> reports the case of a cystic tumor of the cecum met with in a girl of 11 years who died from an attack of typhoid fever. At the post mortem a large, soft, fluctuating tumor, about the size of a duck's egg, was found occupying the cecum and distending slightly the gut. It arose from the anterior wall just above the level of the entry of the ileum. On opening the tumor it was found to be a cyst filled with dark, ropy, mucoid fluid. Under the microscope the outer layer was seen to be mucous membrane similar to that lining the large intestine. The inner layer was much thinned and appeared to resemble a serous membrane, but the writer qualifies this in a foot-note by adding that the epithelial lining of such a cyst was probably mucous in character, but would be much modified by the distention and its appearance still further altered by death. In all probability, he says, it was a retention cyst and further adds that he knew of no similar case, and those whom he consulted were unable to give any reference to cases of like nature.

A. Krogius<sup>2</sup> reports a case of an intestinal cyst in a child 2 months of age, giving rise to obstruction and intussusception. The abdomen was opened and a resection of the gut with formation of an artificial anus was made. Death took place from hemorrhage. The cyst, which had the character of a retention cyst, was of the size of a pigeon's egg and was situated in the ileum close to the valve.

In his paper, Krogius refers to four previous cases, in which a cyst in the intestinal wall encroached on the lumen of the gut and produced symptoms of obstruction.

1. Sainsbury. Harrington: Trans. Path. Soc., London, 1887, xxxviii. 146.

2. Krogius. A.: Ztschr. f. klin. Med., 1903, xlix. 53.



The first case which he quotes was observed by E. Fraenkel<sup>3</sup> in 1851. An infant, a few days old, developed suddenly symptoms of obstruction of the bowels and died. The autopsy revealed as the cause of the obstruction a cyst 2.5 cm. in diameter close to the ileocecal valve; this appears to have had the characters of a retention cyst.

The second case was noted by Kulenkampff<sup>4</sup> in a 3-year-old boy, in whom, suddenly after a dose of calomel, given for obscure symptoms of

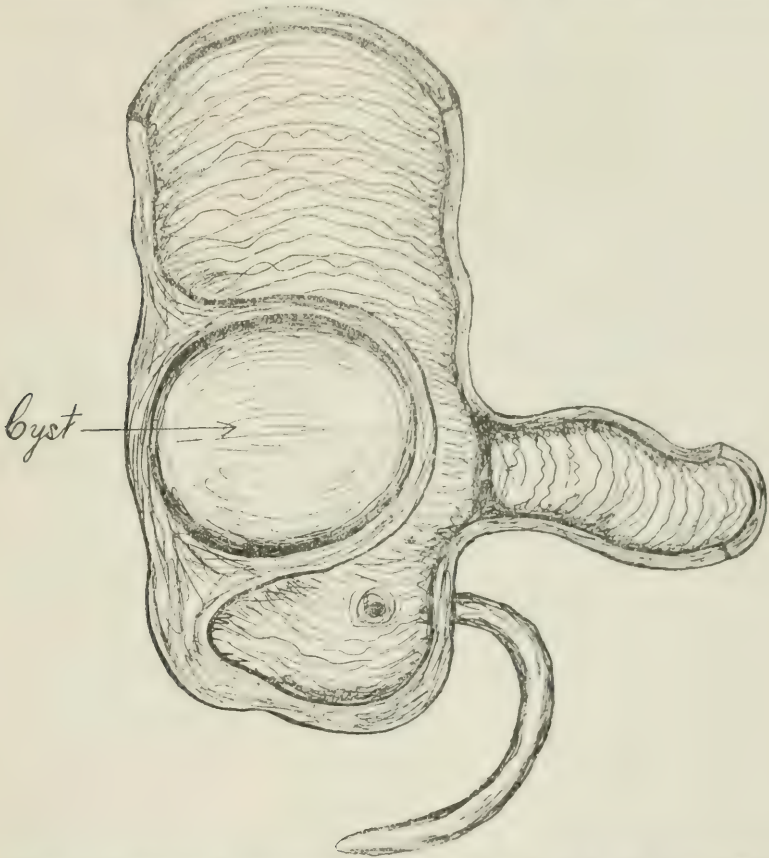


Fig. 1.—Diagram to represent cecum, ileum and cyst cut longitudinally.

obstruction, violent vomiting set in followed by collapse and death. A cyst in the mesentery compressing the ileum appeared to be the cause of obstruction.

The third case was one of obstruction in adult, 62 years of age, due to a cyst which appears to have been of a sarcomatous character.

3. Fraenkel, E.: *Virchow's Arch. f. path. Anat.*, 1882, lxxxvii, 275.

4. Kulenkampff: *Centrallbl. f. Chir.*, 1883, p. 679.

The fourth case, reported by Sprengel,<sup>5</sup> occurred in a girl, 15 years of age, who had had occasional symptoms of temporary obstruction since she was 4 years old. Operation became necessary and revealed a cyst apparently lying between the muscular layers of the intestine, and the apparent cause of an ileocecal invagination. The origin of the cyst was uncertain.

Krogus considers his case to be the fifth reported in which a congenital cyst in the intestinal wall was found to be the cause of occlusion of the bowel.

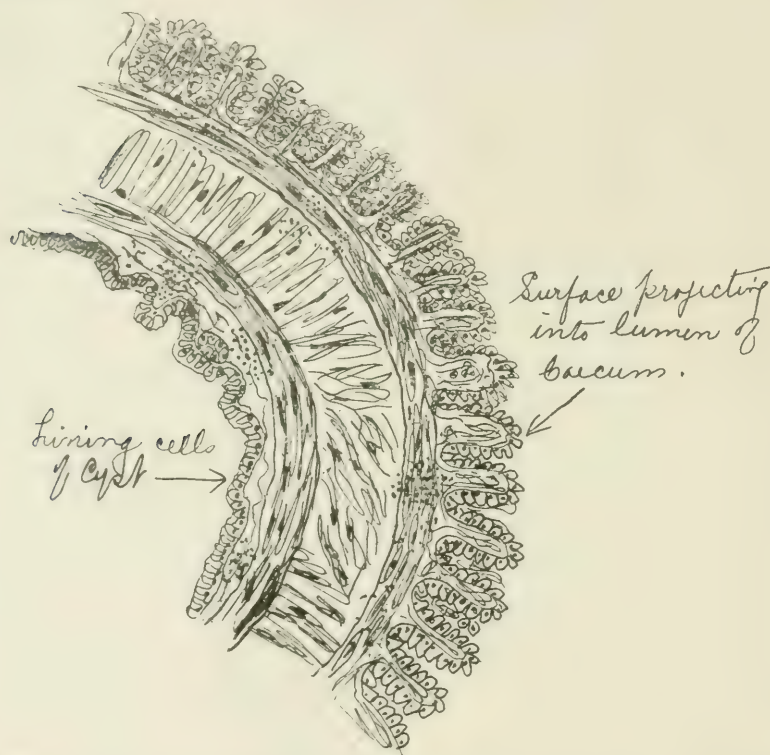


Fig. 2.—Drawing made from section through cyst, showing the internal layer of somewhat flattened epithelium, the three muscular layers, the external mucosa, and the infiltration.

After an extensive search through literature the three cases quoted are the only ones I can find reported of retention cysts in the neighborhood of the ileocecal valve leading to obstruction and invagination.

The following cases have an associated interest, as the clinical symptoms were similar, although the pathological condition had a different origin.

5. Sprengel: Arch. f. klin. Chir., 1900, lxi, 1032.

Chas. A. Morton<sup>6</sup> reports a cyst in the interior of the cecum connected with the base of the appendix, obstructing the lumen of the appendix leading to a cystic dilation of it also. It does not appear, however, to have been a retention cyst for the mucous membrane of the cecum was said to terminate in a ridge around its base. The cyst projected into the lumen of the gut about 1½ inches and was full of amber-colored jelly. Its interior is said to have been smooth, and microscopic examination revealed no mucous membrane covering it or lining its cavity.

Neupert,<sup>7</sup> at the meeting of the Berlin Surgical Society, July 14, 1910, reports the case of a boy 10 years old, admitted to the hospital with a painful circumscribed swelling in the ileocecal region. On opening the abdomen a tumor about the size of a hen's egg was found in the ileum 10 cm. from the ileocecal valve. The tumor occupied the opposite side of the bowel to the mesentery, narrowing the lumen of the bowel. Its surface was smooth and its consistence tense and elastic. Numerous swollen glands were found in the corresponding mesentery. Resection of the gut was performed. The tumor was found to contain sterile pus. Sections of the wall examined microscopically showed a layer of cubical epithelium with traces of a submucosa; tubular glands were absent. Externally and internally the cyst was enclosed by the muscular layer of the intestinal wall. It was therefore regarded as a suppurating cyst, evidently of congenital origin and probably connected developmentally with the omphalo-mesenteric duct.

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6. Morton, Chas. A.: *Bristol Medico-Chirurg. Jour.*, 1887, xv, 319.

7. Neupert: *Zentralbl. f. Chir.*, 1910, p. 714.

# CARDIAC DISEASE IN CHILDHOOD, WITH SPECIAL REFERENCE TO PROGNOSIS \*

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In 1906 I reported the results of an investigation of certain clinical aspects of rheumatic fever in childhood, which was based on a series of 300 consecutive patients admitted to the wards of the Children's Hospital. Of these 300 patients, 209 were discharged from the hospital with signs of organic valvular disease of the heart. The after history of these cases appeared to me to be a point of great interest, with a practical value bearing directly on the question of prognosis, and on certain aspects of treatment. I determined at the time to keep in communication as far as possible, with all of these discharged patients, and at the same time the scope of the investigation was extended beyond the limit of cardiac disease of rheumatic origin, by including all other patients of cardiac disease admitted to the hospital during the period from which the original series was taken. Cases of patients who subsequently died from intercurrent infection were thrown out.

One of the features of greatest interest in such an investigation is the amount of disability carried into adult life, or at least young adult life, by these patients. It was therefore necessary to follow the after-history of these patients for a period sufficiently long to afford evidence on this point. The period in which the cardiac patients of this series were admitted to the hospital was that of a number of years previous to the summer of 1903. I resolved to follow the cases discharged from the hospital until all of them should have entered at least young adult life, taking the age of 14 years as the termination of childhood. All of these patients have now passed this limit, the youngest survivor having reached the age of 15 years.

## ETIOLOGY

The series of cases included in this investigation numbers 304 cases of cardiac disease. It throws a certain amount of light on the relative frequency of occurrence of the various etiologic factors.

TABLE 1.—ETIOLOGY IN CARDIAC DISEASE

	Cases.	Per Cent.
Rheumatic fever .....	264	87
Congenital lesions .....	21	7
Some recognized infection other than rheumatic fever .....	9	3
Unknown etiology .....	10	3

\* Submitted for publication May, 1913.



In compiling this table, in the absence of any laboratory or bacteriologic proof of the existence of rheumatic fever as a specific disease entity, the following clinical evidence of the rheumatic origin of the lesions was employed. All cases which had either during the attack in the hospital, or in previous, or in subsequent attacks, shown symptoms of arthritis or of chorea were classified as manifestations of rheumatic fever. In addition, certain cases of acute endocarditis and pericarditis with fever, in which the clinical picture was precisely similar to other cases in which arthritis did occur, and in which there was no evidence of any other form of infection, were also included. On this basis of classification, no case of acute febrile cardiac disease fell under the heading of unknown etiology, every such case being either due to rheumatic fever, or to some other recognized infection. The cases of unknown etiology were all cases of chronic endocarditis.

The table shows the overwhelming preponderance of rheumatic fever as a cause of cardiac disease.

#### THE CARDIAC CASES DUE TO RHEUMATIC FEVER

*Acute and Chronic Cases.*—Patients entering a hospital with cardiac disease, are admitted either on account of symptoms connected with the disease from which they are suffering, or the cardiac lesion is discovered accidentally in connection with the investigation of their illness. In the 264 rheumatic cases, all patients were admitted because of symptoms of this disease, either arthritic or cardiac. Arthritic symptoms in rheumatic fever, under the present most generally accepted theories of the etiology of this disease, may always be regarded as evidence of the existence at the time, of an active infection. Cardiac symptoms, on the other hand, may occur from two causes. They may be due to the existence at the time of an active infection localized in the heart, or they may be due to the so-called broken compensation, caused by calling on a damaged heart to perform a work which is too great for its power. All the cases in the series which had, during their stay in the hospital, symptoms of arthritis, or in which the cardiac symptoms were accompanied by the regular febrile course characteristic of an acute infection, are classified as acute infections. Those cases in which the cardiac symptoms were unaccompanied by fever, and in which there was no history of an immediately preceding febrile attack, are classified as chronic endocarditis.

The relative proportions of acute and chronic cases in the series are shown in Table 2.

TABLE 2.—PROPORTION OF ACUTE AND CHRONIC CASES

	Cases.	Per Cent.
Acute Infection .....	206	78
Chronic endocarditis .....	58	22

It appears, therefore, that in childhood, the causes which lead a patient to seek hospital treatment, are more often the symptoms produced by the acute infection with rheumatic fever, than those produced by its after-effects on the heart.

*Relation of Cardiac Symptoms to Infection.*—In my former paper I expressed the view that in childhood, as distinguished from adult life, cardiac symptoms are more often due to an actual present infection localized in the heart, than to the overstraining of a permanently damaged heart. I believe that the converse of this view is also true. In adult life, the development of an acute endocarditis in the course of an attack of rheumatic fever, is usually described as an insidious process, manifesting itself by the development of an endocardial murmur. In childhood the occurrence of an acute endocarditis is usually accompanied by actual symptoms referable to the heart. The set of symptoms called cardiac, such as precordial pain, palpitation, cough, dyspnea, orthopnea and eventually enlarged liver and edema, are in adults almost always attributed to overstrain. In childhood, this train of cardiac symptoms undoubtedly may be due to this cause, but in the majority of cases it is due to the existence of an actual present cardiac infection. Of course the symptoms are due to an inability of the heart properly to perform its work, but the cause of this inability is to be found in a fresh cardiac infection. The incompetence of the heart is not dependent on the actual amount of valvular insufficiency or stenosis present, for it bears little or no relation to the lesion. It is probably due to the acute myocarditis; which is known to be a frequent, if not an almost invariable, accompaniment of acute rheumatic endocarditis. The accompanying tables give evidence of the relation of cardiac symptoms to the presence of an actual infection:

TABLE 3.—CASES ADMITTED FOR CARDIAC SYMPTOMS

	Cases
Acute infection present .....	100
Acute infection absent .....	37

This consideration is of interest in reference both to prognosis and treatment, for it is recognized that the cause of death in the majority of these cases is cardiac failure. If the symptoms leading to such failure are most frequently due to infection, or reinfection, and not to overstrain, this fact has an obvious practical bearing.

In any event I wish to deprecate the use of the term broken compensation as applied to the train of cardiac symptoms described under this name when they occur in childhood. Apparently in only a relatively small number of cases is this term, and the theory on which it is based, applicable to the clinical picture as seen in childhood. In the majority of cases, the cause is not overexertion, but fresh infection. The term

cardiac insufficiency is far preferable to broken compensation, as it is equally applicable to both causes.

*The Cardiac Lesions.*—The relative frequency of occurrence of the various cardiac lesions is of interest in connection with the subsequent history of these cases. The relation of the form of lesion to prognosis is still a more or less unsettled question in the cardiac disease of childhood. The cases, classified on the basis of the lesions shown during their stay in the hospital, were as shown in Table 4. In only two cases was pericarditis found without any evidence of a valvular lesion in addition. The fifty-eight cases of pericarditis are classified both as pericarditis and according to the endocardial lesion present, and fifty-six of them are counted twice.

TABLE 4.—OCCURRENCE OF THE VARIOUS CARDIAC LESIONS

	Cases
Mitral insufficiency alone .....	165
Mitral stenosis alone .....	5
Aortic insufficiency alone .....	1
Mitral insufficiency and stenosis .....	79
Mitral and aortic insufficiency .....	8
Mitral insufficiency and stenosis with aortic insufficiency .....	4
Pericarditis .....	58

*Liability in Childhood to Recurrent Attacks of Rheumatic Fever.*—

The liability in any child attacked by rheumatic fever to recurrent attacks is probably the most important factor in all considerations of the prognosis of the disease. In my first paper the liability to recurrence could only be judged on the basis of the history of attacks of rheumatic fever previous to the one under treatment in the hospital. At present, additional evidence is available, from the following of the subsequent history of the patients throughout the remainder of their childhood, and into adult life, through a period of at least nine and one-half years.

TABLE 5.—SHOWING PROPORTION OF RECURRENCES

	Cases
Died in the first attack .....	17
Recovered without recurrence .....	47
Recurrent attacks .....	200

It will be seen that more than one attack of the rheumatic fever infection occurred in 76 per cent. of the cases. Only 17 per cent. showed no recurrence, as in the remaining 7 per cent. no conclusions could be drawn.

*Mortality.*—The complete investigation of this series of cases seems to me to be of considerable value in connection with the question of the mortality in children with hearts attacked by the rheumatic fever infection. The mortality of the cases in the hospital affords a basis for estimating the liability to death in any one attack of the disease. This is shown in Table 6.



TABLE 6.—IMMEDIATE MORTALITY OF RHEUMATIC CARDIAC DISEASE

	Cases
Died in hospital .....	55
Discharged, relieved .....	209

This gives an immediate mortality of 20 per cent. The immediate mortality apparently varies with the character of the process present, as shown in Table 7.

TABLE 7.—IMMEDIATE MORTALITY IN RELATION TO THE CARDIAC LESION

Acute endocarditis .....	27 out of 148 cases or 12 per cent.
Acute pericarditis* .....	18 out of 58 cases or 31 per cent.
Chronic endocarditis .....	10 out of 58 cases or 17 per cent.

\* In all but two of these cases acute endocarditis was probably also present.

Table 7 also shows how much more frequently death occurs as a result of an acute infection with rheumatic fever, than as a result of the overstraining of a chronically damaged heart. In forty-five of the fifty-five fatal cases the patient died in the course of an attack of acute infection, so that the mortality from this cause is 82 per cent. of the total.

The subsequent mortality of the cases in this series represents the chances against a child who has recovered from the attack of rheumatic fever in which he is first seen, but who is left with an organic cardiac lesion. The figures are shown in Table 8.

TABLE 8.—SUBSEQUENT MORTALITY OF RHEUMATIC CARDIAC CASES DISCHARGED FROM THE HOSPITAL

	Cases
Lost to view .....	29
Alive .....	88
Dead .....	92

This gives a subsequent mortality of at least 23 per cent. of all cases, and if, as is fairer, the cases lost to view are thrown out, the mortality of these cases is 51 per cent.

The final mortality is that of all cases whether death occurred in the original investigation or after the discharge of the patient from the hospital. It represents the general mortality of rheumatic cardiac disease for ten years, and the chances, so to speak, in the next ten years, against any child attacked by rheumatic fever with cardiac involvement. It is shown in Table 9.

TABLE 9.—FINAL MORTALITY OF RHEUMATIC CARDIAC DISEASE

Died .....	147
Lived .....	88

This gives the final mortality as 63 per cent. This of course represents, not the mortality of rheumatic fever, but only of the cases of rheumatic fever in which the heart is affected. During the period from which the figures of this paper were taken, only 17 patients with rheu-



matic fever were discharged from the hospital without evidence of a cardiac lesion. Of these 17 patients, 5 remained well, 5 were lost to view, and 7 had recurrence of acute infection with cardiac involvement. Of these latter, 3 died. Including the 12 cases of rheumatic fever which could be followed, the final mortality of rheumatic fever in childhood is 60 per cent.

*Relation of Mortality to Age and to Acute Infection.*—This relation is one of the most interesting results of the present investigation. The basis on which the conclusions are drawn is shown in Table 10.

TABLE 10.—RELATION OF MORTALITY TO AGE AND TO ACUTE INFECTION

	Total	Acute	Chronic
Died before 14 years.....	140	109	31
Died after 14 years.....	7	1	6

In this table the cases placed under acute are those in which the patient died in an acute febrile attack, while those placed under chronic died from cardiac failure apparently following the weakening of the heart from overstrain. It appears from the table that a great majority of the patients died as the result of an attack of rheumatic fever, and not as a result of chronic endocarditis. Even among the ninety-two patients who died after their discharge from the hospital, the majority, sixty-five, died in, or shortly after, an acute febrile attack. Such an attack was the cause of the cardiac symptoms producing death. Therefore not only the figures showing the immediate, but also those showing the final, mortality of rheumatic cardiac disease, point to infection as the chief cause of death.

But when the age at which death occurred is considered, the results are of still greater interest. The average age of all the patients at the time of the original investigation was 9 years. Therefore, ten years having elapsed since, at least an equal amount of childhood and young adult life has been lived by these patients. As more than ten years have elapsed since the majority of the original records were taken, more years have been spent over than under 14 years. Nevertheless, the table shows that the great majority of the patients in which a fatal ending occurred, died while still in childhood. Of the ninety-five patients who passed their fourteenth year, only seven have died, while 140 patients died in childhood. These results surely suggest that rheumatic fever is a vastly more serious and fatal disease in childhood.

The significance of the particular valvular lesions present during the patients' stay in the hospital in connection with the mortality of rheumatic cardiac disease does not appear to be great. The study of the valvular lesions in the fatal cases is not conclusive, because of the great preponderance of mitral insufficiency. The only result which is at all

suggestive, is that no patient in whom the aortic valve was affected is now alive.

I believe there are three causes of the very great mortality of rheumatic fever in childhood. First, the greater liability of children to be attacked with rheumatic fever; second, the greater liability of children to recurrence; third, the greater liability of children to cardiac involvement. I cannot give figures in support of all these statements, but the facts are well known to most pediatricists. Table 10 shows that only one patient died after 14 years of age as the result of recurrent acute infection, the other six dying from chronic endocarditis. But 109 patients died under 14 years of age as the result of an acute infection.

We can only conclude that the chief danger in children with rheumatic cardiac disease is in childhood. The danger of death even from chronic endocarditis is greater, as thirty-one out of 140 patients died of chronic endocarditis in childhood, whereas six out of ninety-five patients died from this cause in young adult life. The chief cause of the danger during childhood, however, is the liability of children to recurrent attacks, in which an acute infectious process localized in the heart is the cause of the cardiac insufficiency leading to a fatal ending.

*The Disability Following Rheumatic Cardiac Disease Acquired in Childhood.*—This is a question of the greatest importance. The survival of eighty-eight patients now under observation, all of whom have entered young adult life, gives a basis for conclusion. The amount of disability is shown in Table 11.

TABLE 11.—DISABILITY IN CARDIAC DISEASE ACQUIRED IN CHILDHOOD OBSERVED IN YOUNG ADULT LIFE

	Cases
Disability great .....	2
Disability slight .....	9
Disability none .....	77

The patients with great disability are unable to work or to lead normal lives. Both of them have been in an adult hospital with broken cardiac compensation. Cardiac symptoms are brought on by comparatively slight exertion. The patients with slight disability have dyspnea on exertion, and some have occasional cough and slight edema. None of them has had an attack of severe broken compensation. They are able to work at sedentary occupations. Seventy-seven patients have no disability. Most of them work, and all of them are apparently leading perfectly normal lives, having had no cardiac symptoms since their childhood. My last set of reports contain many references to activity in dancing on the part of the girls, and in basketball and baseball on the part of the boys. One of the latter asked my permission to enter the twenty-five-mile marathon race. All of these eighty-eight patients still

had their cardiac murmurs when I last saw them. The relation of the amount of disability to the particular valvular lesion is shown in Table 12.

TABLE 12.—RELATION OF DISABILITY TO THE VALVULAR LESION

Great disability .....	2 patients have mitral insufficiency
Slight disability .....	8 patients have mitral insufficiency
	1 patient has mitral insufficiency and stenosis
No disability .....	56 patients have mitral insufficiency
	19 patients have mitral insufficiency and stenosis
	2 patients have mitral stenosis

When the relative occurrence of the various lesions is taken into account, this table shows no relation between the amount of disability and the character of the valvular deformity.

The relation of the amount of disability to the age at which the patient had his first attack of rheumatic fever is shown in Table 13.

TABLE 13.—RELATION OF DISABILITY TO AGE OF FIRST RHEUMATIC ATTACK

Disability	Age in First Attack, Years	Number of Cases
Great .....	12 and 13	2
Slight .....	10 to 14	9
None .....	2 to 6	50
	6 to 10	20
	10 to 14	7

This table shows that all the patients with disability were attacked when past the age of 10 years, whereas in the cases without disability, the majority were first attacked in early childhood. It suggests that the earlier in childhood a cardiac lesion is acquired, the better will be the result as regards the ability to lead a normal adult life.

It seems to me that the general amount of disability seen in rheumatic cardiac disease acquired in childhood is remarkably small. I believe it to be very much less than the disability following rheumatic endocarditis acquired in adult life. Unfortunately, I cannot give figures bearing on this point, as, while rheumatic fever is fairly common in adults, it attacks the joints alone with such greater frequency than in childhood, that cases in which endocarditis develops for the first time in adult life are comparatively rare. I have not had time to accumulate a sufficient number of such cases to afford a basis for comparison. I believe, however, that such a comparison would show a much less disability in cardiac disease acquired in childhood. My recollection of my work in an adult out-patient department, and in a general hospital, is that the majority of patients suffering from broken compensation or serious disability from chronic endocarditis, could trace the origin of their lesion, if at all, to some attack of rheumatic fever occurring since they had entered adult life. On the other hand, in every adult out-patient department are seen many patients who are seeking medical aid



on account of some affection other than cardiac, in whom, in the course of routine examination, some valvular lesion of the heart is found. In a large number of cases these patients declare that they have never suffered from cardiac symptoms, and have no recollection of any attack of rheumatic fever. I believe that in very many of such patients, the cardiac lesion represents the sequela of an attack of rheumatic fever which occurred in childhood, at an age when the arthritic manifestations are often or so much less pronounced, that they are not remembered. These patients, leading normal lives, yet with every evidence of organic cardiac disease, are common. They correspond to the seventy-seven cases in my series in which no cardiac disability persisted.

A possible explanation of this lessened disability in cardiac disease acquired in childhood, is suggested by the inferences from Table 13. The disability appears to be less, the earlier in childhood the lesion is acquired. In many of the permanent lesions acquired in childhood, the power of adaptation between the damaged organ and the work required of it is greater, and children show a marvelous power of adapting themselves to the requirements of life. In the case of cardiac disease, I believe the so-called compensation of the damaged heart is more than a mere mechanical hypertrophy. I believe that when the lesion occurs during childhood, that is, during the period of active growth, a mutual adaptation between the heart and the child gradually occurs, which is far more perfect than can occur after the period of growth is passed. The child grows up to fit its heart, and the heart develops to fit the child. Only in this way can I explain the facts suggested by this paper. The earlier in life the damage to the heart, the longer is the period of growth during which this adaptation can occur.

*Inferences as to the Treatment of Cardiac Disease of Rheumatic Origin.*—The outcome of the patients discharged from the hospital is suggestive as regards treatment. Treatment in the chronic endocarditis of childhood resolves itself largely into the question of prophylaxis. If the sole danger to be apprehended were the rupture of compensation by overstrain, prophylaxis would consist simply in the guarding of children with damaged heart valves from overexertion. But we have seen that the chief danger lies in the liability to a recurrent attack of the infection. We know so little of the exact nature of the infecting organism in rheumatic fever, and of its channels of invasion, that we can accomplish comparatively little in preventing recurrent attacks, beside the most general hygiene measures. The evidence in favor of the tonsil as a frequent route of invasion is so great, that, in view of the fatality of the disease, I believe we are justified in advocating the removal of the tonsils in every patient who has had one attack. If a patient who, in addition to having had an attack of rheumatic fever, is subject to tonsillitis, removal



of the tonsils is positively indicated. The frequency and severity of rheumatic fever appears to vary somewhat with climate and locality. Whenever it is possible, I believe we should lessen the chances of reinfection by removing the patients to a place where rheumatic fever is uncommon.

The most important question is how far we should go in guarding against the breaking down of cardiac compensation by overstrain and overexertion. That children are liable to danger from this cause is a fact, as shown by the thirty-one patients in this series who died from chronic endocarditis while still within the limit of childhood. That we should endeavor to guard against dangerous overstrain goes without question. But it is questionable how far our efforts should reach in limiting the normal activities of the child. We must consider the question of lessening the disability in adult life, when the heart must be able successfully to cope with the strain of a normal active life. If such ability is due to a gradual adaptation between the child and the heart, it is very probable that too much limitation of the activities of childhood will prevent this adaptation from taking place, and will leave the child unfitted to encounter the demands of active adult life.

Most of the parents of the patients in my series were given strict directions as to the guarding of their children from overstrain, and as to the limiting of their activities. Some of them followed these directions, while the majority disregarded them entirely. Singularly enough, of those who obeyed these directions at all, the majority obeyed them with exaggeration, limiting the activities of the children to an extreme degree. The relation of the limitation of activity to the mortality from chronic endocarditis is shown in Table 14.

	Carefully Guarded	Normal Activity
Died, 37 .....	13	24
Lived, 88 .....	20	68

The proportion of children who lead a life of normal activity during childhood is greater in those who lived than in those who died. It does not seem from this series at least as if the guarding of children from overexertion had any notable effect on the mortality. Moreover, when the cases are analyzed as to the relation between limitation of activity and subsequent disability, it appears that in general those children did better in whom the normal activities of childhood were not limited at all.

I do not mean that we should let our cardiac patients engage in all normal activities without limit, or without supervision. I simply wish to point out the possibility of going too far toward the other extreme. I believe we should avoid putting our cardiac patients under a glass case,

for even normal activity is preferable to extreme limitation of activity. We should remember the other aspect of the question, that of the gradual adaptation of the child to the damaged heart, which takes place during the previous period of growth. We must do all in our power to favor this process, and this can only be done by allowing the heart to accustom itself to increasing demands on its power during this period. Nothing can be more important than the proper management of these cases, for I believe that the future of the child is largely dependent on it. The most thorough supervision is essential. Beginning at an early period after the disappearance of symptoms, with passive motion against increasing resistance, we should constantly increase the amount of activity allowed, by regulated exercises, so long as we can keep within the danger limit, of which the warning signs are extreme rapidity of cardiac action, or slight dyspnea. But we should not stop when a moderate amount of activity can be indulged in without symptoms. We should continue to increase the amount of activity allowed, and if finally these children can indulge in all the activities of childhood without symptoms, I believe we should not hesitate to remove all limitations. Their chief danger during childhood lies in reinfection, not in overexertion, and the more they learn to do in childhood, the better are their prospects for a normal, active, useful adult life.

#### CONGENITAL CARDIAC DISEASE

The cases of congenital cardiac disease in this series are too few to permit the drawing of conclusions of any great value. There were twenty-one cases.

*Open Ductus Arteriosus.*—Fifteen cases were diagnosed as open ductus arteriosus. The patients had a murmur, but no enlargement of the cardiac dulness. Two of them had slight cyanosis but no thrill, and two had a palpable thrill but no cyanosis.

The final result in these cases was as follows: Two died, four were lost sight of and nine recovered. The two patients who died, were those having slight cyanosis, and who died in infancy. In one the diagnosis was confirmed at autopsy. Both of the cases in which there was a palpable thrill recovered, with disappearance of the thrill. In all of the nine cases of recovery, and in two of the patients lost sight of, the murmur eventually disappeared, but I am unable to state the exact time of its disappearance. The nine patients are now apparently well, and are between 10 and 16 years of age.

*Pulmonary Stenosis.*—Five cases were diagnosed as pulmonary stenosis. The patients had a murmur, cyanosis, palpable systolic thrill and enlargement of the area of cardiac dulness. Of these cases, four patients died before they were 2 years old, and one recovered. This patient is still very cyanotic, with the same signs and clubbed finger tips.

*Deficient Ventricular Septum.*—In one case this diagnosis was made. There was a murmur, enlargement of the cardiac dulness, no cyanosis and no thrill. This patient, seen at 8 months, lived a year, and was then lost sight of.

It would seem that open ductus arteriosus is a comparatively favorable lesion. The most interesting feature is the disappearance of the murmur in the patients who recovered. As open ductus arteriosus is due to a failure of the closing of the ductus by normal obliterating endarteritis, I believe the disappearance of the murmur suggests that the closure is simply delayed, and may normally occur later. In these cases, without thrill, cyanosis, or enlargement, I believe that as far as the cardiac lesion is concerned, a most favorable prognosis should be given.

#### ENDOCARDITIS OF OTHER ORIGIN THAN RHEUMATIC FEVER

Beside the congenital cases, there were only nineteen cases of endocarditis in the series which could not be connected with the rheumatic fever infection. Of these, ten cases were of unknown origin. Rheumatic fever could not be excluded, but no connection with this infection was found either in their past or subsequent history. Of these cases, four patients were lost sight of, three entered adult life with signs of mitral insufficiency, but no disability, and in the remaining three the murmur disappeared and they are well.

Of the nine remaining patients, two were fatal cases of purulent pericarditis following pneumonia, and two were fatal cases of malignant endocarditis following an alveolar abscess and mastoiditis, respectively. In the other five cases the cardiac lesion was attributed to scarlet fever. Two of the patients were lost sight of and three have no disability. In one of these the murmur has disappeared.

#### CONCLUSIONS

1. Rheumatic fever is very much the commonest cause of cardiac disease in childhood.

2. Cases with acute rheumatic infection localized in the heart are much commoner than cases suffering from chronic endocarditis.

3. Cardiac symptoms are due to two causes: first, acute infection localized in the heart; second, broken cardiac compensation. Of these two causes the first is the commoner.

4. The liability of children to recurrent attacks of acute rheumatic infection, in any of which the heart may be involved, is very great.

5. The immediate mortality of rheumatic cardiac disease is about 20 per cent.

6. The subsequent mortality of patients with endocarditis of rheumatic origin, followed for at least ten years in about 50 per cent.



7. The final mortality of rheumatic fever followed for at least ten years is 60 per cent.

8. The mortality is seen chiefly during childhood. The mortality after young adult life is reached falls to only 7 per cent.

9. The cause of death is heart failure. The cause of the heart failure may be either acute cardiac infection or broken compensation. In childhood the former cause is far the more common. After adult life is reached the latter cause is more common.

10. The particular valvular lesion present has little or no relation either to the mortality or the amount of disability in adult life; except that aortic disease appears to be a particularly fatal lesion in childhood.

11. The causes of the great mortality of rheumatic fever in children are, first, their greater liability to this infection; second, their greater liability to recurrent attacks; third, their greater liability to cardiac involvement.

12. Patients who escape the dangers of childhood, and who enter adult life, are apt to show a remarkable freedom from disability. The majority of such patients can lead normal active lives.

13. The probable cause of this freedom from disability lies in the fact that the cardiac damage occurs during the period of growth, and during this period a particularly perfect adaptation can take place between the heart and the patient, which enables the heart to meet the demands made on it. This adaptation is more perfect than can be attained in the adult.

14. The earlier in life the cardiac lesion is acquired, the better is apt to be the result in adult life, as concerns ability to lead an active, normal existence: provided that the patient escapes the dangers of childhood.

15. Treatment should be directed toward favoring the adaptation of child and heart. While guarding against overstrain, we must avoid too great limiting of the normal activities of childhood.

16. In congenital cardiac disease, open ductus arteriosus is a favorable lesion.

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## THE DIAGNOSIS AND TREATMENT OF PYELITIS IN INFANCY \*

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The pyelitis of infancy, which is a fairly common disease, is generally understood by pediatricians, as expressed in their writings, as a disease characterized by an active, remitting temperature, and which is treated most successfully by the use of alkalies, while some cases may be cured by hexamethylenamin in doses of  $\frac{1}{2}$  to 2 grains three times a day, or every three hours.

Recent experiences have led me to believe that such statements should be materially modified. We should rather say that the pyelitis of infancy is a disease which is usually characterized by a high remitting temperature, but may give rise to no temperature, and that while some patients may be cured safely by neutralization of the urine with alkalies and others by doses of hexamethylenamin such as those named, that the most efficient treatment in difficult cases is by the use of very large doses of hexamethylenamin aided by vaccines, either commercial or autogenous. In confirmation of this statement I wish to present briefly three cases of pyelitis which I have recently had under observation.

### CASE REPORTS

**CASE 1.**—A healthy female child, 1 year old. One month after a vaccination, which took well, and when it was practically healed the child suddenly had a temperature of 104 F. and examination of the urine showed a pyelitis. Alkaline treatment was prescribed and in four days the urine had cleared and the child had a normal temperature. Nine days later, however, the temperature again arose and the alkaline treatment was prescribed, but after three days, the temperature having gradually risen to 105.6 F., the alkaline treatment was stopped and hexamethylenamin was given in doses of 1 grain every four hours. (Chart 1.) This was changed two days later to 1 grain every three hours and again in two days to 1 grain every two hours, and finally to 1 grain every hour, without any evident effect on the symptoms. The hexamethylenamin was then stopped, it being considered unsafe to continue this dose for many days. Potassium citrate in doses of 5 grains every three hours was again ordered and it neutralized the urine, but under this treatment the temperature began to rise again. At this time a blood examination showed 22,000 white corpuscles, 56 per cent. polynuclears, 3,800,000 red cells and no malarial organisms. The urine drawn by a catheter showed colon bacilli as well as a few colonies of streptococci. Thirty millions of commercial colon vaccines were then administered. Administration of the vaccine was followed in two days by a normal temperature, which, however, quickly reacted up, on the fourth day having reached nearly 102 F., so

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\*Submitted for publication May 15, 1913.

that on the fifth day a second dose of 50,000,000 colon vaccines was administered, followed immediately by a normal temperature.

The child was then put on benzoate sodium with hexamethylenamin, 12 grains of each during the day. The following day this was increased to 15 grains and the day after to 24 grains. On this day, however, the temperature again arose to 101.5 F. On the twentieth day of the disease the child's weight was 21¼ pounds, showing a gain of 2¼ pounds during the preceding four weeks. The child began to gain weight as soon as the temperature was reduced by the vaccines. The following day, the temperature having risen to 101.4 F., 40,000,000 bacteria were again administered with a prompt reduction in the temperature. The urine continued to show many leukocytes and bacteria. Twenty-four grains of hexamethylenamin daily was continued until the twenty-seventh day of the disease when the following report on the urine was received from Dr. F. C. Wood: "The only Gram-negative bacillus which was found was not the colon, as it did not ferment sugar. There were ordinary staphylococci in small numbers. The specific gravity was 1.010. It showed no albumin or diacetic acid, but many leukocytes and bacteria."

All medication was now stopped. Six days later, the temperature having again arisen to 102.2 F., 30,000,000 of the same vaccines were administered. No

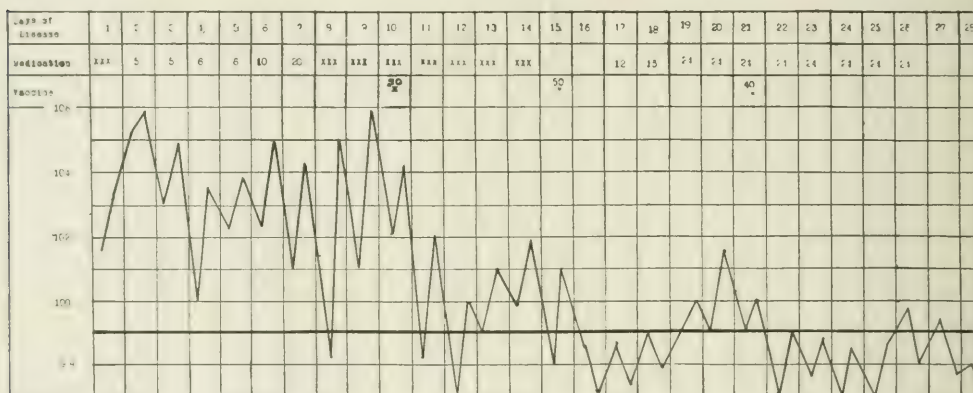


Chart 1.—(Case 1) Temperature curve in an infant with pyelitis. X=millions of vaccine.

further medication was attempted until the forty-second day when it was decided to try the effect of very large doses of hexamethylenamin for short periods. Twenty-five grains daily without sodium benzoate were then given for four days with a marked diminution in the number of leukocytes and bacteria present. On the fifth day this was run up to 30 grains and on the sixth day to 35 grains, with still a diminution in the bacteria and leukocytes, but without obtaining a sterile urine and without any evidence of irritation of the kidneys. There was no albumin in the urine, and no diacetic acid. On the fifty-fourth day of the disease, after a week without treatment, 40 grains of hexamethylenamin were administered with an improvement in the urinary condition, and on the following day 40 grains and the third day 45 grains, at which time the urine was found to be sterile. Treatment was then stopped and no recurrence of the urinary infection has occurred during the year that has passed.

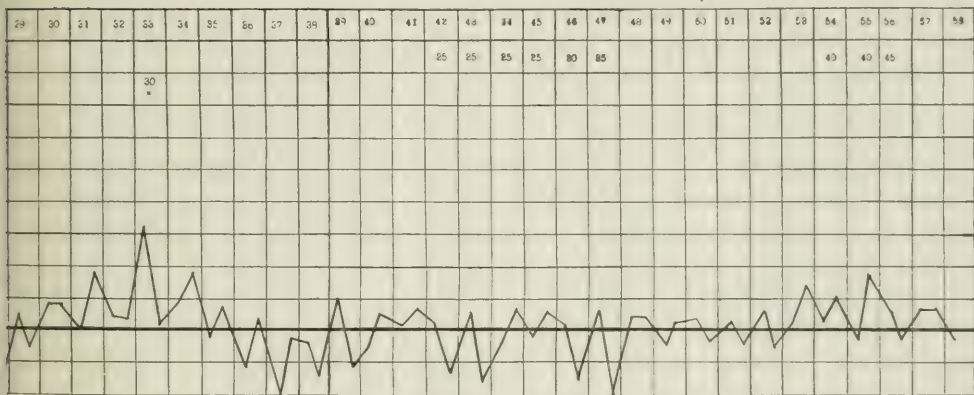
These large doses of hexamethylenamin neither caused any evidence of disturbance of the kidneys nor any interference in the well-being of the child. As soon as the fever was controlled by the vaccines the child

gained in weight and really seemed better when on large doses of hexamethylenamin than at any other time.

CASE 2.—It is interesting to note the long period of lack of fever and constitutional symptoms, but with a continuation of the pyelitis as evidenced by pus and bacteria in the urine after the administration of vaccines, especially in connection with the next case of which I wish to speak in which a similar infection of the urinary tract with colon bacilli occurred in a child 9 months old, who seemed apparently well at the time the urinary infection was found. This child had been under my care since birth and had never had a febrile disturbance.

Dec. 21, 1912, I found that the urine of this apparently healthy child was moderately acid, had a specific gravity of 1.015, contained a faint trace of albumin, a moderate amount of acetone, a faint trace of phenol, clumps of pus and many bacteria; some in chains. The child was put on potassium citrate, 5 grains every three hours. A specimen taken by catheter showed a pure culture of colon bacilli.

After five days of this alkaline treatment, there being no improvement in the condition of the urine,  $\frac{1}{2}$  grain of hexamethylenamin was ordered to be given every three hours, so that the child got three grains that day, on the twenty-



Arabic numerals = grains of hexamethylenamin. Roman numerals = grains of citrate of potash.

seventh 5 grains, on the twenty-eighth 10 grains, on the twenty-ninth 12 grains, on the thirtieth 15 grains, and 18 grains on the thirty-first. During this time the urine continued to contain leukocytes and bacteria, the leukocytes varying in number from 12 to 50 in a D field. On January 1, 20 grains of hexamethylenamin were administered, on the second 25 grains, and on the third 30 grains. This dose was continued until the sixth of January, when the urine still continued to be contaminated. The hexamethylenamin was stopped and potassium citrate was again administered. The contamination of the urine continued under this treatment, although several times the urine appeared almost free from contamination, and on this account the alkaline treatment was continued longer than it otherwise would have been. On January 27 four doses of 7 grain each, or 28 grains of hexamethylenamin were given, and on the twenty-eighth 35 grains, on the twenty-ninth 35 grains. On the thirtieth macules appeared on the body, especially adjacent to the upper part of the diaper, and the child had a temperature of 101 F. the night before. She was not taking her bottles very well and had lost  $\frac{1}{2}$  pound in four days and the hexamethylenamin was stopped.



With these large doses of hexamethylenamin the urine rapidly cleared and the day after it was stopped a specimen of urine was found to be sterile and no contamination of the urine has since occurred.

This case, then, of colon pyelitis without temperature in an 18-pound baby was cured by 35 grains of hexamethylenamin a day for three days without any evidence of irritation of the kidney or marked interference of the general health. Whether the macules on the body, the loss of half a pound in weight, and the slight rise in temperature were due to the hexamethylenamin I am unable to say.

No vaccines were used in this case as vaccines appear to control the constitutional symptoms and to have little or no control over the inflammation.

CASE 3.—A third case was recently seen by me in consultation with Dr. Thomas F. Lancer. A female child, 6 months old, had been sick six days. On the day preceding the one when I saw the child the temperature had reached 106 (Chart 2). There was a pause at the end of inspiration and an expiratory grunt, and the movements from the bowels contained some mucus.

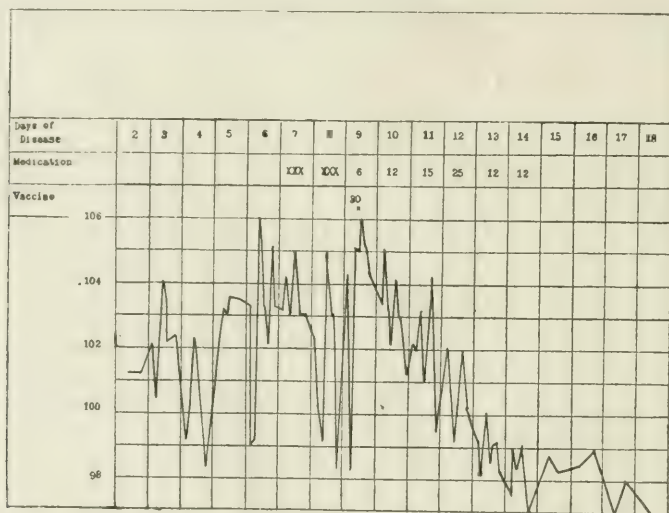


Chart 2.—(Case 3) Temperature curve in an infant with pyelitis. X=millions of vaccine. Arabic numerals=grains of hexamethylenamin. Roman numerals=grains of citrate of potash.

By a system of exclusion a probable diagnosis of pyelitis was made, and the child was put on potassium citrate. An examination of the urine showed a colon pyelitis. After three days on potassium citrate, although the temperature had been lower, the child looked much worse and the temperature arose again to 106 F. Thirty million colon bacilli were then administered and 6 grains of hexamethylenamin were given on this day. No immediate marked decline in temperature followed the administration of vaccines. The following day 12 grains of hexamethylenamin were given, on the eleventh day 15 grains, on the twelfth day 25 grains, and on the thirteenth day the temperature was normal and the urine was sterile.

No disturbance of the child's health was caused by the large doses of hexamethylenamin, 25 grains a day in a 6-months' baby. The urine never contained more than a faint trace of albumin.



## CONCLUSIONS

Pyelitis in infancy, due to the invasion of the pelvis of the kidney with colon bacteria resulting in a purulent inflammation, can apparently occur with no perceptible rise of temperature at any time. These cases should be treated and cured by the means ordinarily used in pyelitis.

The alkaline treatment of pyelitis, while it is safe and will control many cases, is markedly less efficient than other methods of treatment.

Vaccines, either autogenous or commercial, are useful in controlling the constitutional symptoms of pyelitis.

Hexamethylenamin, while sometimes effective in doses of from  $\frac{1}{2}$  to 2 grains several times a day, will not in these doses cure certain cases which may be controlled by very large doses.

Hexamethylenamin should always be administered in small doses first, but the dose should be rapidly run up, the child and its urine being carefully watched for symptoms of irritation of the kidneys.

Large doses of hexamethylenamin should not usually be continued for more than a week at a time, and then after several days without any treatment or with alkaline treatment it should be started at the maximum dose given before and the amount increased daily until an influence on the urine is obtained. Doses of 25 grains daily in a child of 6 months, and from 35 to 45 grains a day in a child from 9 to 12 months may be safely given in this way to some infants.

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## ANALYSIS OF ONE THOUSAND CASES OF EPIDEMIC MEASLES \*

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Measles may be said to be nearly endemic in communities of children by reason of the regularity of its appearance at certain seasons of the year, and its peculiar partiality for definite age periods. Amongst the diseases of childhood it is conspicuous at times for its great mortality where associated with conditions of poverty and overcrowding. The small, spasmodic outbreaks which occur amongst an urban population may be said to be cyclical, and depending on the arrival of a number of children at the susceptible age period. These localized epidemics are not in themselves of importance from the point of severity or complication; the attack is generally mild and the healthy child does not suffer from complications or resulting ill effects. The seasonal outbreak of measles of a low type of virulence is a different disease from that witnessed at times in the fulminating epidemics. In these the manifestation is of a wide and rapidly spreading nature, and its potentialities for immediate and remote physical mischief to the child, are much increased. The infecting agent seems to become aggravated as the cases increase in number, complications become constant and severe, instead of occasional and mild, and the tendency to serious sequelae is much enhanced. The mortality at these times is sometimes very high, particularly in institutions for children (15 to 35 per cent., Holt); on the other hand, a lower rate pertains in homes where the necessity for keeping a number of children of susceptible age in close association does not exist (4 to 6 per cent., Holt).

During the years 1910 and 1911 outbreaks of measles of an exceptional nature occurred amongst the emigrant children arriving in the port of New York. It was believed that an account of these cases would be of interest as possessing certain unusual features of their own, as well as from the large number under observation at the Hoffman Island Isolation Hospital during that period.

For the proper appreciation of the factors underlying the occurrence among a certain class of an epidemic disease of exceptional severity, there should be first considered the physical condition of the individual, including also the nature of his environment, before and at the time of attack; the number of cases among a susceptible community and the

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\* Submitted for publication April 25, 1913.

severity of the symptoms move in a kind of arithmetical progression with the sum of the conditions that produce ill health. That this is a truism is well borne out by experiences of war and disaster. In the great stream of emigration that sets in toward the United States at certain seasons of the year, the emigrant child is borne along, always a helpless victim of the flow of world populations. If we inquire into the circumstances of this child emigration we will find that after being taken from the home village, the discomforts of a long railway journey (at minimum rates) constitute only the beginning of a long period of hardship before sailing. Frequently there is a detention in observation camps for many weeks, in an environment far from resembling the home life, and a certain exposure to every form of infectious disease.

Although the law requires that none but healthy children of emigrants be allowed to embark with their parents, even the healthiest children cannot readily adapt themselves to the changed conditions of life on board ships. To meet this new experience, the emigrant child after weeks of privation has little or no store of resistance to draw on for any emergency. The proper amount of fresh air and exercise, so necessary to young people who have lived in the open, cannot always be obtained in stormy weather at sea, and this is a very frequent occurrence in the North Atlantic during the two or more weeks voyage from the Mediterranean ports. The parents themselves are often so prostrated with seasickness that they are unable to care properly for the children. The unavoidable crowding in confined spaces and the concurrent weakness resulting from seasickness all tend to render the emigrant child particularly susceptible to infectious disease. It is among material of this nature that quarantine experience shows the epidemic disease of childhood assumes a gravity little known in communities ashore. The following tables and figures presented here are taken from the records of a thousand cases of epidemic measles occurring among emigrant children treated at Hoffman Island Isolation Hospital during nine months of 1910-1911.

#### SEASONAL INCIDENCE

Reference to Table 1 will show that most of the cases occurred in December and April, May and June. The annual summer and winter maxima are well accentuated, the number being 186 for June and 145 for December, respectively. Nearly half the total number occurred in the three months April, May and June.

#### SEX INCIDENCE

The sexes were very evenly balanced, the numbers being 490 male, 510 female.

## AGE INCIDENCE

The age incidence of attack varies somewhat from that usually recorded in measles. The greater number appears in the three-year age period, 195 (Tables 3 and 4); the two-year period ranking next with 166, and the under-one-year period third with 140. The number of cases under one year is unusually high. Three years and under contribute 603 cases (60.3 per cent.); over ten years the number is 48; over twenty years, 10.

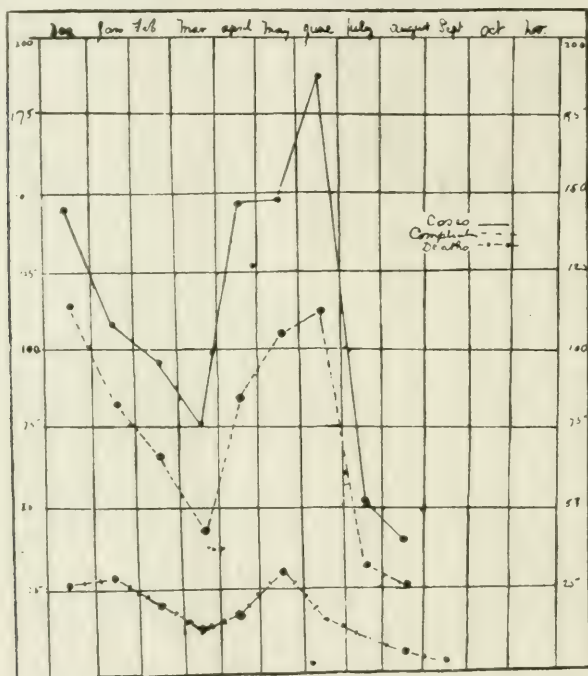


Chart 1.—Monthly curves of cases and incidence of complications and deaths in 1,000 cases of measles.

## THE COMPLICATIONS

The index of the severity of a measles outbreak depends on the number and character of the complications, and it is to these alone that the high mortality at times is due. The disease being essentially one whose outward manifestation is a catarrh of the mucous air passages, it is by the various continuation of these into special parts that the complications arise. In this epidemic the outstanding feature was the occurrence of purulent otitis media in 495 cases, of which 353 were affected in both ears. To place the occurrence of the otitis under the various age periods we found that, one year and under, 42.9 per cent. of the cases



TABLE 1.—NUMBER OF CASES, COMPLICATIONS AND MORTALITY, ARRANGED ACCORDING TO MONTHS, IN 1,000 CASES OF MEASLES

Month	Cases	Complications	Mortality	Month	Cases	Complications	Mortality
January .....	107	78	27	July .....	51	32	10
February .....	97	68	21	August .....	44	26	6
March .....	75	44	12	September .....	...	..	3
April .....	147	84	14	November .....	...	..	..
May .....	148	105	28	October .....	...	..	..
June .....	186	113	18	December .....	145	114	26

TABLE 2.—PERCENTAGE OF COMPLICATIONS AND DEATHS IN EACH MONTH

Month	Cases	Percentage of Complications	Percentage of Deaths	Month	Cases	Percentage of Complications	Percentage of Deaths
December ....	145	78.6	17.9	May .....	148	70.9	18.9
January .....	107	72.8	25.2	June .....	186	60.7	9.6
February ....	97	70.1	21.6	July .....	51	62.7	19.9
March .....	75	58.6	16.0	August .....	44	59.0	13.0
April .....	147	57.1	9.5				

The above table shows graphically the number of measles cases in each month with the percentage of complications and fatal cases. Greatest percentage of complications occurred in the four months of December, January, February and May. June with the greatest number of cases had a small complication incidence and the smallest case mortality of all the months but April. The months of January and February show the highest case mortality, 25.2 and 21.6 per cent., respectively.

TABLE 3.—NUMBER OF CASES, COMPLICATIONS AND MORTALITY IN 1,000 CASES OF MEASLES ARRANGED ACCORDING TO AGE

Age	Cases	Complications	Mortality	Age	Cases	Complications	Mortality
Under 1 year...	140	101	43	6 years .....	54	33	8
1 year .....	102	83	36	7 years .....	42	32	0
2 years .....	166	111	37	8 years .....	32	18	1
3 years .....	195	127	24	9 years .....	20	9	0
4 years .....	122	77	10	10 years .....	9	3	0
5 years .....	70	42	6	Over 10 years.	48	29	12

TABLE 4.—PERCENTAGE OF COMPLICATIONS AND DEATHS AT EACH AGE PERIOD

Age Period	Cases	Percentage of Complications	Percentage of Deaths	Age Period	Cases	Percentage of Complications	Percentage of Deaths
Under 1 year...	140	72.1	30	6 years .....	54	61.1	14.8
1 year .....	102	81.3	34.3	7 years .....	42	76.1	....
2 years .....	166	66.8	22.2	8 years .....	32	56.2	3.1
3 years .....	195	65.1	12.3	9 years .....	20	45.0	....
4 years .....	122	63.1	8.1	10 years .....	9	33.3	....
5 years .....	70	60.0	8.5	Over 10 years ..	48	60.4	4.1

The above table shows the number of cases occurring in each age period with the percentage of complications and deaths. The one-year period shows the greatest incidence of complication and deaths. The first three age periods show more than twice the number of fatal cases of all the other age periods combined.

TABLE 5.—CAUSES OF DEATH IN AGE PERIODS

Disease	Under 1 yr.	Years										Over 10	Total
		1	2	3	4	5	6	7	8	9	10		
Bronchopneumonia . . .	10	3	6	3	3	..	..	..	..	..	..	1	26
Bronchopneumonia and otitis media . . . . .	1	1	7	4	1	1	2	..	..	..	..	..	17
Bronchopneumonia and diphtheria . . . . .	9	4	6	2	3	1	3	..	..	..	..	..	23
Bronchopneumonia, diphtheria and otitis media . . . . .	4	2	4	2	4	..	2	..	..	..	..	..	18
Bronchopneumonia and enteritis . . . . .	12	19	7	1	..	..	..	..	..	..	..	..	39
Bronchopneumonia and pertussis . . . . .	2	1	2	1	..	..	..	..	..	..	..	..	6
Bronchopneumonia and cellulitis . . . . .	..	..	..	..	1	..	..	..	..	..	..	..	1
Lobar pneumonia . . .	..	..	..	1	..	..	..	..	..	..	..	..	1
Empyema . . . . .	1	1	1	4	1	..	..	..	1	..	..	1	10
Diphtheria and otitis media . . . . .	..	1	..	1	..	..	..	..	..	..	..	..	2
Disseminated tuber- culosis . . . . .	1	2	..	..	..	1	..	..	..	..	..	..	4
Pyemia . . . . .	1	..	..	..	..	..	..	..	..	..	..	..	1
Mastoiditis and sepsis	..	..	..	..	..	1	..	..	..	..	..	..	1
Enteritis . . . . .	3	1	1	..	1	..	..	..	..	..	..	..	6
Noma . . . . .	..	1	1	..	..	1	..	..	..	..	..	..	3
Tonsillar gangrene and sepsis . . . . .	..	..	..	..	..	1	1	..	..	..	..	..	2
Peritonitis, acute sup- purative . . . . .	..	..	..	..	..	1	..	..	..	..	..	..	1
Marasmus . . . . .	1	..	..	..	..	..	..	..	..	..	..	..	1
Totals . . . . .	45	36	35	19	14	7	8	0	1	0	0	2	167

were affected. Two years 51.2 per cent. Three years 52.89 per cent. Four years 54.0 per cent. Five years 47.1 per cent.

Otitis media as a complication in so large a number of the cases tended to increase the severity of the complications and sequelae of measles, the possibilities of septic infection and of long suppurative processes being much increased under these conditions. The day of onset of the otitis was found to be variable; although the membrana tympani might be found red and congested during the first week, indications of pus were not usually found before the tenth or twelfth day of the disease. This was at times accompanied by a rise in the temperature, but an active suppurative process could proceed with little or no indication in the temperature chart. After paracentesis and irrigation, temperature and clinical symptoms subsided rapidly.

Nearly a quarter of all the cases, 20.4 per cent., developed a bronchopneumonia as a severe and typical complication — 204 cases. Enteritis and ileocolitis were present in 156 cases; this was an especially fatal complication in children of one year and under. Along with bronchopneumonia it accounted for 23.3 per cent. of the total deaths. The deaths from bronchopneumonia and enteritis numbered 39, of which 31 were of one year and under. Cervical adenitis, 78 cases, was frequently associated with a lymphadenitis of the axilla or submaxillary area.

Scarlatina as a complication of measles occurred forty-five times. Where measles occurred as a complication of scarlatina, it was recorded as a plain measles case. Mastoiditis, 47; of these, 42 were operative and 8 were double infections. Capillary bronchitis was present in 17 cases and lobar pneumonia in 11.

Acute nephritis as a late manifestation occurred in 7 instances, usually at the twentieth to the thirtieth day. Although these cases had not been clinically observed as having suffered from a concurrent scarlatina, it could not be altogether excluded as a causative factor.

Three cases of noma and 2 of tonsillar gangrene were recorded, all ending fatally. Vaginitis was present in 50 cases. A number of these were of gonorrheal origin, as shown by positive examination of vaginal swabs. Diphtheria was a frequent complication, especially among the very young children — 143 cases; including diphtheria of the nose alone, 23; throat and nose, 10; eye, 5. Diphtheria with bronchopneumonia and otitis media were responsible for 28.7 per cent. of the total deaths. Measles with hemorrhagic rash, 3 cases with one death. Empyema, following bronchopneumonia or simple pleurisy, 13 cases, with 10 deaths. Pyemia with multiple abscesses, 2 cases, with one death. Purulent conjunctivitis, 16. Abscesses, 32 (including 12 of the scalp). Impetigo, 11.

## THE FEVER IN MEASLES

The fever in uncomplicated measles is not high, usually running between 103 and 104 F. The duration of the fever after the appearance of the rash may be variable and its undue extension dependent on very slight causes in children. In 24 cases observed, the average duration was two days, in 128 cases it was three days, and in 236 cases it was four days. If the temperature remains high after the fourth day, or a continued hyperpyrexia has been present from the beginning, a grave complication is almost certain to supervene.

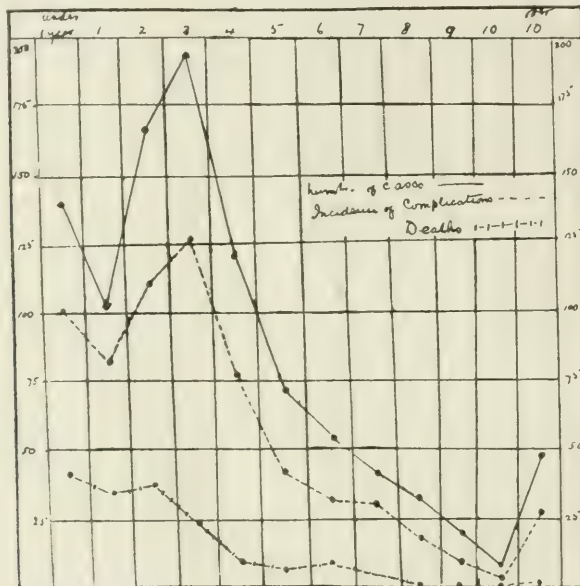


Chart 2.—Age, curves of incidence of cases, complications and mortality.

## FATALITY OF HIGH TEMPERATURE IN MEASLES

For the purpose of obtaining some information as to the ratio between temperature and mortality in measles, the following observations were made:

Highest temperature not over 102 F.,	128 cases, 1 death, mortality	0.78 Pct.
Highest temperature between 102-103 F.,	87 cases, 4 deaths, mortality	4.5 Pct.
Highest temperature between 103-104 F.,	145 cases, 5 deaths, mortality	3.4 Pct.
Highest temperature between 104-105 F.,	198 cases, 40 deaths, mortality	25.2 Pct.
Highest temperature between 105-106 F.,	121 cases, 45 deaths, mortality	37.2 Pct.
Highest temperature between 106-107 F.,	28 cases, 15 deaths, mortality	53.5 Pct.
Highest temperature over 107 F.,	1 case, 1 death, mortality	100 Pct.

From the above it will be seen that the liability to a fatal issue increases directly with the rise in temperature. It is also noteworthy that 46.5 per cent. of the 28 cases with a temperature reaching between



106 an 107 F. recovered. An initial high temperature does not always indicate a severe attack of the disease.

#### THE INCIDENCE OF COMPLICATIONS

It will be seen by Tables 1 and 2 that the greatest monthly percentage of complications occurs in December and January, showing that in every hundred cases of measles in those months, 78.6 and 72.8 per cent. of them suffered from complications. June, with the greatest number of cases, had a small complication incidence, 60.7 per cent. The incidence of complications for the age periods are shown in Tables 3 and 4. It will be seen that the one-year age period shows the highest percentage of complications, in that every hundred cases of measles at that age had complication in 81.3 per cent. of them.

#### MORTALITY

The total number of deaths was 167; case mortality 16.7 per cent. The causes of death for the age periods are given in Table 5. By far the greatest number of fatal cases are due to bronchopneumonia in association with some other complication. With enteritis the number is the largest, 39; with diphtheria, 28; bronchopneumonia alone, 26; with otitis media, 17; empyema, 10, and enteritis alone, 6. The greatest case mortality is in the one-year age period, 34.3 per cent. (Table 4). The first three age periods together show more than twice the number of fatal cases of all the other age periods combined. After 3 years the case mortality decreases enormously. Case mortality is nearly equal for both sexes. The greatest monthly case mortality occurs in January, 25.2 per cent., and February, 21.6 per cent. April has the lowest monthly case mortality, 9.5 per cent. (Table 2).

#### SEQUELAE

Pertussis was the most frequent of the sequelae, 32 cases being recorded. Miliary tuberculosis occurred in four cases, with four deaths. A right-sided hemiplegia of face and eyelid was observed in a female child, aged 1 year, on the thirty-second day of the disease. Recovery took place.

#### SUMMARY

Of the 1,000 cases of measles the greatest number were in the month of June (186).

The third year age period shows the greatest incidence of attack (195). The largest complication percentage, 81.3, and case mortality, 34.3 per cent., are found in the first year period.

The seasonal prevalence of complication was highest in December, 78.6 per cent., and of case mortality in January, 25.2 per cent.

The most frequent complication was otitis media, 495.

The most common cause of death, bronchopneumonia and enteritis, 23.3 per cent. of total deaths. Average duration of the fever, four days. The onset of purulent otitis media on tenth or twelfth days may not be attended by unusual fever. If the temperature remains high after the fourth day, a possible grave complication is imminent. An initial high temperature does not necessarily point to a possible severe attack.

I am indebted to Dr. S. B. Ragsdale of the Quarantine Staff for assistance in the preparation of the figures on the fatality of high temperature in measles.

# PROGRESS IN PEDIATRICS

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## RÉSUMÉ ON THE CIRCULATORY SYSTEM

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### HEART-BLOCK

The incident of heart-block in acute infectious diseases such as diphtheria, typhoid fever, pneumonia, influenza and endocarditis, is recognized, since the use of polygraphic tracings, as being more and more frequent. Sudden death is not infrequently due to lesions of the a-v bundle; and many cases of bradycardia, especially in diphtheria, are unquestionably caused by complete or partial heart-block, and not by vagus inhibition.

Hecht<sup>1</sup> emphasizes the importance, for the rendering of the prognosis, of determining whether the heart-block is due to an organic lesion of the bundle fibers, or to a functional inhibition of their conductivity. He mentions two illustrative cases, one of diphtheria, the other of measles. Atropin caused no change in the disturbance of the stimulus conduction, merely increasing the sinus frequency, in the diphtheria case; while the disturbance in the stimulus conduction disappeared almost entirely, after atropin in the case of measles. The disturbed conduction persisted unchanged during four months in the diphtheria case; whereas in the measles case it was replaced as soon as eight days later by a nearly normal behavior, and after three weeks by entirely normal conditions. In view of its transitory character, and its reaction to atropin, the case of measles block must be designated, clinically, as functional. Robinson and Draper<sup>2</sup> have shown by means of the electrocardiograph that in a man with a normal heart, vagus stimulation will cause not only a marked slowing of both auricles and ventricles, but also a depression of conductivity of the heart beat from auricles to ventricles.

### HEART IN DIPHTHERIA

Rohmer<sup>3</sup> studied the heart by means of the electrocardiograph in several cases of diphtheria, to find the relation of anatomical lesions of the atrioventricular bundle to sudden death, and also with the object of investigating whether diphtheritic myocarditis exerts a specific influence

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1. Hecht, A. F.: *Ztschr. f. Kinderh.*, 1912, iv, 546.

2. Robinson, G. C., and Draper, G.: *Jour. Exper. Med.*, 1911, xiv, 217.

3. Rohmer, P.: *Jahrb. f. Kinderh.*, 1912, lxxvi, 391.

on the curve of the electrocardiogram, and if so, how far it may be of prognostic value. Two cases presented clinically the undoubted picture of atrioventricular dissociation, which in one instance could also be demonstrated by means of the electrocardiogram. The heart-block in these two cases appeared two or three days before death and persisted unchanged. The almost complete anatomical integrity of the bundle in these two cases proves that it may be poisoned up to a total loss of its function without this intoxication being anatomically demonstrable. Rohmer believes that specific relations to the diphtheria toxin do not exist and that diphtheritic heart death is not due to an elective damage of the His bundle, although the loss of transmission in a severely affected heart must necessarily act injuriously and make prognosis more grave. Myocarditis in the course of diphtheria produces no change in the electrocardiographic picture unless the heart failure reaches a pronounced degree.

Tanaka,<sup>4</sup> in studying serial sections of the heart in fifteen children dying during or soon after an attack of diphtheria, found that fatty degeneration of the heart muscle was the most important change. The amount of degeneration of the atrioventricular bundle showed no relation to that of the rest of the heart; in some cases the bundle of His showed fatty or hyaline degeneration, while the rest of the myocardium was nearly free from it, and vice versa. Neither did sudden paralysis of the heart have any relation to lesions of the bundle of His.

Price and Mackenzie<sup>5</sup> report a case of heart-block in diphtheria associated with auricular fibrillation. This is the first recorded instance of a case of this kind occurring in diphtheria. The heart muscle showed extreme degeneration, but the sino-auricular node and the auriculo-ventricular node and bundle were not involved. Pepper and Austin<sup>6</sup> have reported a case of complete heart-block in a man 40 years of age, in which there was no demonstrable lesion of the bundle of His, and cite six similar cases previously reported. On the other hand, Cowan, Fleming and Kennedy<sup>7</sup> report two cases of complete heart-block, one diphtheria, the other malignant endocarditis, and three cases of acute endocarditis with nodal rhythm, in all of which the a-v node or bundle was involved in an acute inflammatory process. Butterfield<sup>8</sup> reports a case of heart-block with an acute infection of the whole heart including its membranes. Although the whole heart showed a diffuse inflammatory infiltration it reached its greatest intensity in the auriculoventricular node.

4. Tanaka, T.: *Virchows Arch. f. path. Anat.*, 1912, ccvii, 115.

5. Price, F. W., and Mackenzie, I.: *Heart*, 1912, iii, 232.

6. Pepper, W., and Austin, J. H.: *Am. Jour. Med. Sc.*, 1912, cxliii, 716.

7. Cowan, J., Fleming, G. B., and Kennedy, A. M.: *Lancet*, London, 1912, i, 277.

8. Butterfield, H. G.: *Heart*, 1912, iii, 203.



## SYPHILIS

Recent work of Warthin<sup>9</sup> shows that syphilis plays a rôle in the etiology of heart disease, the importance of which has heretofore been unsuspected. In the study of a large number of cases of congenital syphilis, he has found fatty degeneration of the heart muscle present in every case, either as a diffuse fatty change or a focal process. The diffuse fatty change is found in the more severe cases of diffuse interstitial change and is associated with the cellular infiltration, fibroblastic proliferation and myxomatous stroma of this form of syphilitic myocarditis. In lesions of this type, spirochetes are always found in great numbers. The focal fatty areas may occur independently of any infiltration or proliferation, or of any vascular obliteration. With hematoxylin and eosin preparations these areas suggest simply an edema with fatty degeneration of the muscle fibers, but examination by the method of Levaditi shows the presence of spirochetes. Warthin believes that colonies of spirochetes associated with focal fatty changes alone represent either a milder or a more acute infection. In very mild or latent infections colonies of spirochetes have been found in tissues showing no histologic changes at all.

It seems probable that these parenchymatous lesions may heal without an interstitial reaction, as focal fibroid areas and focal calcification of the degenerate muscle fibers have been found in a late stage of congenital syphilis. The important fact that spirochetes may be found in the heart muscle and in no other organ has been demonstrated in two cases of congenital syphilis.<sup>10</sup> The fact that the heart may show marked lesions in cases of congenital syphilis, when the liver, lungs and spleen show no changes at all and no spirochetes, has a great practical importance in pathologic diagnosis.

In seventeen fetuses and new-born infants known to be syphilitic by the presence of spirochetes in the principal organs, Rebandi<sup>11</sup> found in thirteen of these definite histological changes in the aorta. Even under the low power there is seen an increase in the thickness of the aortic wall, which is chiefly confined to the adventitia and media. The vasa vasorum, some of which appear enlarged and hyperemic, others with a sometimes considerably reduced lumen and abnormally thickened walls, are surrounded by a small cellular infiltration. This infiltration varies in intensity in individual cases, involving the adventitia, the outer layers of the media, very rarely the intima. The lesions are similar to those found in syphilitic aortitis in adults. Spirochetes were found in all cases and their number was in direct proportion to the severity of the pathologic changes. No instance was found in which spirochetes were present

9. Warthin, A. S.: Jour. Am. Med. Assn., 1912, lviii, 409.

10. Warthin, A. S., and Snyder, E. J.: Jour. Am. Med. Assn., 1912, lviii, 689.

11. Rebandi, S.: Monatsschr. f. Geburtsh. u. Gynäk., 1912, xxxv, 681.

without histologic change, as Warthin has found in the heart muscle. In mesaortitis, the presence of the spirochetes must usually, though not always, be considered as the efficient cause, but in certain cases the agent of the arterial affection is probably simply due to the syphilitic toxins. Panaortitis is always due to the presence of spirochetes.

Levy-Frankel<sup>12</sup> concludes that congenital syphilis is the most common cause of chronic aortitis, and also believes that the pathologic changes may be either microbic or toxic. He states that the adrenal glands, in all probability, play an important part in the pathogenesis of certain atheromatous lesions which at first glance appear to be referable to rheumatism or chorea. Hypertrophy and hyperplasia of the medullary layer of the adrenal glands were noted in two cases, in conformity with the findings of Aubertin and Clunet, who pointed out the frequent co-existence of medullary hyperplasia in the adrenals of adults with atheroma.

#### ARTERIOSCLEROSIS

Rittenhouse<sup>13</sup> has confirmed Hamburger's<sup>14</sup> observations on arterial rigidity in children. His conclusions are based on the examination of 250 well children between 2 and 14 years. No rigidity was found in twenty children at the age of 2 years. Below the age of 7 years, rigidity of the arteries was exceedingly rare, but was found in 50 per cent. of the cases between the ages of 7 and 10, and in 80 per cent. of the cases at the age of puberty. Rigidity of the temporal arteries was commonest under the age of 6, while the radial arteries were more often affected from the age of 7 onward. With one exception, all the children in whom a high degree of arterial rigidity was detected, showed nervous symptoms. No relation between high blood-pressure and arterial rigidity was observed.

#### BLOOD-PRESSURE IN INFECTIONS

Rolleston<sup>15</sup> has studied the blood-pressure in diphtheria and scarlet fever and concludes that while sphygmomanometry is of considerable theoretical interest, it is of little practical importance except in the convalescence of scarlet fever when nephritis is a complication. In such a case it may give some indication of the severity of the renal lesion. In only twelve out of thirty-three cases of nephritis, however, was the blood-pressure above normal, and the hypertension never extreme nor of long duration. Findlay<sup>16</sup> found that the older the individual and the higher the blood-pressure, the greater the difference in systolic pressure in the brachial and digital arteries. In childhood and youth the systolic

12. Levy-Frankel, A.: *Arch. d. mal. du cœur*, 1912, v, 625.

13. Rittenhouse, W.: *Wien. klin. Wehnschr.*, 1912, xxv, 920.

14. Hamburger, F.: *München. med. Wehnschr.*, 1911, lviii, 250.

15. Rolleston, J. D.: *Brit. Jour. Child. Dis.*, 1911, viii, 433; 1912, ix, 444.

16. Findlay, L.: *Quart. Jour. Med.*, 1911, iv, 489.

pressure in the digital arteries equals that registered in the brachial artery. In adults, on the other hand, and in diseases accompanied by high blood-pressure, the systolic brachial pressure is much higher than the systolic digital pressure. Consequently, pressure readings with the Gärtner tonometer, while unreliable in adults, are reliable in children, except in cases of high blood-pressure.

#### CONGENITAL HEART DISEASE

In studying, by means of the orthodiograph, the configuration of the heart outline in congenital heart disease, P. and F. M. Groedel<sup>17</sup> have been able to establish certain distinctive radiographic features in the different types of the disease. Defects of the septum may be recognized precisely by the absence of a change in the configuration of the heart outline. A defect in the ventricular septum can be established on the basis of the peculiar ventricular movements of the margin of the right heart shadow, and be distinguished in this way from a patent foramen ovale. The bulging of the pulmonary artery is characteristic of congenital aortic stenosis and persistence of the ductus Botalli. In the case of the latter, the heart appears in mitral configuration (upright); whereas it lies in the form of a cylinder in aortic stenosis. Pulmonary stenosis furnishes no typical shadow. Of all the congenital lesions of the heart a persistent ductus Botalli gives the most typical x-ray picture.

Wessler and Bass,<sup>18</sup> in five cases of persistent ductus Botalli, found the bulging pulmonary artery as described by the Groedels. The heart in pure patent ductus arteriosus shows no enlargement nor alteration in shape. The presence of such changes suggests an associated or complicating lesion. In mitral disease the pulmonary artery may be enlarged, but it does not pulsate as it does in a patent ductus arteriosus. This shows the necessity of making the diagnosis from a fluoroscopic examination.

#### ARRHYTHMIA

Friberger's<sup>19</sup> investigations on arrhythmia in healthy children is of unusual interest. These were conducted on 321 unselected school children, between 5 and 14 years of age, and included an examination of the entire body as well as sphygmographic curves. None of these children presented a perfectly regular pulse. A fairly regular pulse was found in 37.4 per cent., a moderately irregular pulse in 50.4 per cent., and a very irregular pulse in 12.2 per cent. The genesis of the arrhythmia was uniform, in so far as the direct origin of the irregularity must be referred to a point of the stimulus-producing and stimulus-conducting system, situated above the auricle. Three principal forms of arrhythmia were

17. Groedel, P., and F. M.: *Deutsch. Arch. f. klin. Med.*, 1911, ciii, 413.

18. Wessler, H., and Bass, M. H.: *Am. Jour. Med. Sc.*, 1913, cxlv, 543.

19. Friberger, R.: *Arch. f. Kinderh.*, 1912, lviii, 30.



noted: (1) In the majority of cases, long pulse beats alternated with shorter ones in such a way that the duration of the wave is gradually lengthened during a few beats, after which it again becomes gradually shortened; (2) the frequency is suddenly retarded at irregular intervals and then gradually increases again; (3) appearance of disorderly, irregular beats, which are about 0.1 second longer or shorter than their neighbors.

The cases not infrequently presented certain irregularities which agreed in no way with the above-noted principal manifestations of juvenile arhythmias, but rather suggested the idea of extra-systoles, or omitted systoles respectively. In all the curves showing pictures suggestive of extra-systoles, or of sino-auricular block, a distinct respiratory arhythmia was demonstrable, at least for certain distances; this as well as the extra-systoles may possibly have the same genesis. In no case examined was the respiratory type of arhythmia altogether absent, and the establishment of this fact is believed to be not devoid of value for the interpretation of the genesis of juvenile arhythmia.

The higher degrees of arhythmia are usually found in the younger children. Among children 5 to 6 years old, only 14.3 per cent. had a fairly regular pulse; among the 12-year-olds, 58.0 per cent. had such a pulse; among the 14-year-olds, 50.0 per cent. Arhythmia was found to be only slightly more common in girls. Height, weight and muscular development seemed to exert no influence on the frequency of arhythmia. With special reference to the condition of the circulatory organs it is noteworthy that arhythmia occurs more often with abnormally high, or abnormally low pulse rates, than with the rate which is the rule for that particular age. In a selected group of thirty-four children, presumably having weak hearts, arhythmia was about as frequent as in the rest of the material. Among nervous children it was only slightly more common than in others. Among children whose hemoglobin was 70 per cent. or less, 98 per cent. showed arhythmia. In children with habitual symptoms of gastro-enteric disease, arhythmia is not more common than in other children. The pulse of children varies not only in regard to frequency, but also as to volume, although not to a marked degree. The chief result of this investigation consists in the demonstration of the presence of arhythmia in all children between 5 and 14 years of age, so it must be considered as being physiological. Juvenile arhythmia is not a transitory, variable phenomenon, but represents a fairly constant property of the individual in whom it is found. Concerning the causative factors which determine the various degrees of the arhythmia, the findings fail to afford much information. The age is undoubtedly of importance, as is also the condition of the blood. On the other hand, no special influence seems to belong to differences in bodily development, a mild degree of cardiac weakness, or instability of the nervous system.



## INDEX TO CURRENT PEDIATRIC LITERATURE

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### ANATOMY AND PHYSIOLOGY

- Albumin Content and Electric Conductibility of Infant's Blood, Fluctuations in.—  
O. Hagner.  
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- Gland, Previously Undescribed, in Thymus Region with an Internal Secretion.—  
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- Banti's Disease in Children.—A. D'Espine.  
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- Infants' Blood, Fluctuations in Albumin Content and Electric Conductibility of.—O. Hagner.  
Ztsch. f. Kinderh., July 12, 1913.
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Arch. Pediat., May, 1913.
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Centralbl. f. d. Grenzgeb. d. Med. u. Chir., May 23, 1913.

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# American Journal of Diseases of Children

Vol. 6

SEPTEMBER, 1913

No. 3

## DYSPITUITARISM

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### HISTORICAL

Vesalius was the first to describe the pituitary, and in his "De Corporis Humani Fabrica" he named it the "glands pituitam excipiens"; he believed that this gland secreted the nasal mucus (*πρωϊτα*, phlegm). However, Galen many years before him knew of this gland, and judging from its well protected location, thought it was of great importance to the human economy. In 1778, Soemmering described it more fully and called it the "hypophysis cerebri." Both Vesalius and Soemmering were of the opinion that the pituitary is a gland; but as they could not find any duct, they considered it a part of the nervous system. Wepfer, Bonnet (1679) and Morgagni found colloid cysts in the pituitary, and Greding (1771) and Melcrave observed and described enlargements of the pituitary. Wenzel claimed that diseases of the pituitary may cause epilepsy; and in the light of present knowledge this is true; for many cases suffering from dyspituitarism have manifested epileptiform seizures.

In 1838, Rathke<sup>1</sup> discovered the dual origin of this gland from the floor of the third ventricle and from a diverticulum of the pharynx (Rathke's pouch). In 1840, Mohr demonstrated the relation of adiposity to tumors of the hypophysis. In 1860, Liégeois,<sup>2</sup> studying the anatomy of this organ, added it to the list of the ductless glands. Marie<sup>3</sup> and Marinesco reported two cases of acromegaly in 1886, and although they were mistaken, in that they thought this disease was due to hyposecretion of this gland, they were the first to draw attention to the relationship between this disease and changes in the hypophysis. About this time Launois described gigantism, and thought that some of these cases may be due to diseases of the pituitary; but it was Cunningham, who, in 1891, had proved that gigantism and acromegaly are the same disease, the only difference being that gigantism was the result of

1. Rathke, H.: Ueber die entstehung der Glandula pituitaria. Arch. f. Anat. Physiol. u. wissensch. Med., 1838, No. 5, 482.

2. Liégeois: Anatomie et Physiologie des glandes vasculaires sanguines, Paris, 1860.

3. Marie, P.: Sur deux cas, d'acromegalie. Rev. de méd., 1886, vi, 297.

pituitary disease in cases where the epiphyseal centers had not yet ossified, and acromegaly in cases where ossification had taken place. In 1899 Oppenheim<sup>1</sup> recognized the importance of x-ray examinations of the sellar region as an aid in diagnosis of tumors of the pituitary. Although Pechkranz correlated adiposity with abnormal skeletal changes, with anomalies of the hypophysis, and although Babinski<sup>5</sup> reported a case of tumor of the pituitary without acromegaly in 1900, Fröhlich<sup>6</sup> is usually given the credit of describing this type of dyspituitarism, in spite of the fact that his communication did not appear until 1901. To Cushing<sup>7</sup> (1909) is due the credit of putting our knowledge of the secretion of the pituitary on a scientific basis; it is he who pointed out and clearly stated the functions of the individual lobes and showed that clinically we may have many different types, depending on whether one or both lobes are hypo- or hypersecreting. In 1912, Burnier<sup>8</sup> collected a group of cases in which dwarfism is associated with hypophyseal symptoms; he refers to them as cases of "Hypophyseal Nanism."

Sir Victor Horsley was the first to publish a personal note regarding the experimental removal of the gland; however, the first actual contribution was made by Marinesco (1892); he concluded that the loss of the whole gland was compatible with life for a long time. The first studies which include any suggestive observations on the symptomatology of a pituitarism were published in 1892, and in 1894 by Vassale and Sacchi; among others who experimented were Cyon, Caselli, Friedmann, Maas and von Eiselsberg.<sup>9</sup> The most important contribution was made in 1908 by Paulesco<sup>10</sup> of Bucharest; he found that removal of the anterior lobe is equivalent to removal of the entire gland (i. e., death in

1. Oppenheim: Discussion, *Arch. f. Psychiat.*, 1901, xxxiv, 303.

5. Babinski, J.: Tumeurs du corps pituitaire sans acromégalie et avec arrêt de développement des organes génitaux, *Rev. neurol.*, 1900, yiii, 531.

6. Fröhlich, A.: Ein Fall von Tumor der Hypophysis Cerebri ohne Akromegalie, *Wien. klin. Rundschau.*, 1901, xv, 883.

7. Crow, S. J., Cushing, H., and Homans J.: Experimental Hypophysectomy, *Bull. Johns Hopkins Hosp.*, 1910, xxi, 127; Effects of Hypophyseal Transplantation, *Quart. Jour. Exper. Physiol.*, 1909, ii, 389; Cushing, H.: Sexual Infantilism with Optic Atrophy in Cases of Tumor Affecting the Hypophysis Cerebri, *Jour. Nerv. and Ment. Dis.*, 1906, xxxvi, 704; The Hypophysis Cerebri: Clinical Aspects of Hyperpituitarism and of Hypopituitarism, *Jour. Am. Med. Assn.*, 1909, liii, 249; Partial Hypophysectomy for Acromegaly, *Ann. Surg.*, 1909, 1, 1002; The Functions of the Pituitary Body, *Am. Jour. Med. Sc.*, 1910, xxxix, 473; 1913, cxlv, 313; Diseases of the Pituitary, 1912; Cushing H., and Goetsch, E.: Concerning the Secretion of the Infundibular Lobe of the Pituitary Body and Its Presence in the Cerebrospinal Fluid, *Am. Jour. Physiol.*, 1910, xxvii, 60.

8. Burnier: Hypophyseal Nanism, *Ann. Ophthal.*, January, 1912.

9. Eiselsberg, F. v.: Discussion *Wien klin. Wchnschr.*, 1909, xxii, 287; Operations on the Hypophysis, *Tr. Am. Surg. Assn.*, 1910, xxviii, 55; *Am. Surg.*, 1910, lii, 1; *Arch. Chir.*, 1912.

10. Paulesco, N. C.: *L'hypophyse du cerveau*, Paris, 1908, Vigot Frere.

twenty-four hours); that loss of the posterior lobe led to no appreciable disturbances, and that separation of the stalk from the base of the brain amounted to a complete or nearly complete removal, as the case might be. In the same year (1908) appeared the notable work of Herring<sup>11</sup> on the anatomy and the histology of the pituitary.

The first operations on the hypophysis were by Horsley;<sup>12</sup> the operative procedure in attacking the hypophysis has been studied on cadavers by Lowe and Koenig, Jr., but has been cleared essentially by Schloffer,<sup>13</sup> who also operated on the first patient on the continent in March, 1907.

#### ANATOMY OF THE PITUITARY

The pituitary body is found in all vertebrates; the development of this gland begins very early in embryonic life. The pituitary is a small reddish-gray, vascular mass of an oval form, situated in the sella turcica, where it is retained by a process of dura mater; this process covers the sella turcica and has a small hole in its center through which the infundibulum passes. The pituitary has a dual origin, the cerebral part develops from a hollow protrusion which comes down from the floor of the third ventricle; the ectodermic portion originates from a diverticulum of the pharynx (Rathke's pouch) which passes upward and unites with the cerebral portion to form the adult gland. As development goes on the anterior or lower part of the closed sac becomes thickened, forming the anterior part of the pituitary body. A more or less definite cleft separates this portion from the posterior lobe, which is composed of the cerebral portion and of the upper portion of the primitive closed sac; these two parts become closely adherent and remain functionally associated; thus the neural part becomes surrounded by an intimate epithelial investment possessing a different histological picture from that which characterizes the anterior lobe, though the two are of ectodermic origin. The epithelial investment of the posterior lobe, together with its upward extension on the outer walls of the infundibular stalk, is designated the *pars intermedia*. During fetal life the posterior lobe contains a cavity which communicates through the infundibulum with the cavity of the third ventricle; in the adult it becomes firmer and more solid, and the cavity is replaced by lymph-channels, surrounded by cells; these lymph-channels empty directly into the cavity of the third ventricle.

11. Herring, P. T.: The Histological Appearance of the Mammalian Pituitary Body, *Quart. Jour. Exper. Physiol.*, 1908, i, 121; The Development of the Mammalian Pituitary and Its Morphological Significance, *Ibid.*, p. 161; A Contribution to the Comparative Physiology of the Pituitary Body, *Ibid.*, p. 261.

12. Horsley, V.: On the Technic of Operations on the Central Nervous System, *Brit. Med. Jour.*, 1906, ii, 411.

13. Schloffer, H.: Zur frage der Operationen an der Hypophysis, *Beitr. z. klin. Chir.*, 1906, l. 767.

In the cat the posterior lobe retains throughout life its original cavity in free communication with the third ventricle of the brain; the parts which are derived from the buccal epithelium form an almost complete investment for the nervous portion, and the original lumen of the epithelial pouch also persists throughout life in the form of a well-marked cleft.

The pituitary of the monkey more closely resembles that of man, and is a type in which greater fusion of the original elements from which it has developed has taken place. The posterior lobe is solid throughout. Its investment by the epithelial portion is not so complete as it is in the cat, and only a small cleft remains as the representative of the original buccal pouch.

The pituitary in man is therefore composed of a large anterior lobe (*pars anterior*), composed entirely of epithelial tissue; of a posterior lobe (*pars nervosa*) which is of neural origin, and of an intermediate portion (*pars intermedia*), which, though of neural origin, becomes invested by and intimately fused with a portion of the epithelial sac.

The anterior lobe consists of large granular cells and numerous blood-vessels; the protoplasm of some of these cells being receptive to eosin, some to hematoxylin and some barely staining at all; it is a gland producing an internal secretion, which is poured directly into the blood. The *pars intermedia* is composed largely of neutrophilic elements. The posterior lobe is made up of two structures; of these the part developed from the brain and consisting of neuroglia and ependyma cells and fibers acts as a framework; it is more or less surrounded and invaded by epithelium which probably furnishes its active part; the secretion passes into the lymph-vessels and is destined to enter the ventricles of the brain.

The *pars anterior* is very vascular,<sup>14</sup> and the *pars nervosa* is poor in blood-vessels. The anterior lobe receives its blood-supply from about eighteen or twenty small arteries which converge toward the stalk from the various components of the circle of Willis; these vessels immediately break up into numerous large sinusoidal spaces, in apposition with the cells, and are lined only by endothelium; hence there are no veins or arteries proper in the anterior lobe.

The *pars intermedia* derives its supply from the vessels of the stalk, from the adjacent brain and from the posterior lobe. The posterior lobe receives its arterial supply from a small artery formed by the union of symmetrical branches from each internal carotid.

According to Creutzfeldt,<sup>15</sup> the hypophysis in the new-born is cylindrical, and its dimensions are, sagittal diameter 5 mm., frontal 9 to 11 mm., vertical 2 mm., and its weight is 90 to 150 mg.; at 10 years it

14. Dandy, W. E. and Goetsch, E.: The Blood-Supply of the Pituitary Body. *Am. Jour. Anat.*, 1911, ii, 137.



assumes a more oval form, mostly due to growth of anterior lobe; it continues to grow to 30 years, is stationary until 40 to 50 years, and then begins to decline. In adults it has an oval form and is larger in women than in men; its weight is 550 to 800 mg.; the sagittal diameter is 6 to 10.5 mm., the frontal 10 to 14.5 mm., and the vertical 5.9 to 9.75 mm.

Erdheim and Stumme<sup>16</sup> examined 150 glands of pregnant women; they noted a color change from gray-red to white, and an increase in size and weight of the structure (900 to 1,800 mg.).

#### EXPERIMENTAL DATA

The researches of Goetch, Cushing, Jacobson,<sup>17</sup> Crowe and Homans,<sup>7</sup> and Weed, Cushing and Jacobson,<sup>18</sup> have put our knowledge of the physiology of the pituitary on a firm foundation. On the whole, they were able to confirm the findings of Paulesco. They discovered that total removal of the gland in adult dogs causes death in two or three days, with symptoms of cachexia hypophysipriva; in puppies death does not follow for ten days (three to twenty). The symptoms of cachexia usually do not appear for twenty-four to forty-eight hours after the removal of the gland; a marked diminution of urinary output, even to anuria and a transient glycosuria may occur immediately after operation in adult dogs; and in puppies a post-operative polyuria has been often observed, contrasting with the opposite condition seen in the adult dogs. The symptoms of cachexia are unsteadiness of gait and lowered body temperature; an awkward arching of the back, with incurvature of the tail is characteristic; later there is still further fall of temperature, slow respiration, slow pulse, irregular muscular contraction, tremors, lethargy, anesthesia, coma and death; the temperature just before death may fall 20 C. Grafts in cases of total removal cause a distinct prolongation of life through this means.

The effects of posterior lobe removal are inconclusive; some of the dogs had convulsive attacks with maniacal excitement and persistent erotomania.

The results of partial removal of the anterior lobe are the same if the posterior lobe is removed also. In puppies such removal leads to

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15. Creutzfeldt, H. G.: Ein Beitrag zur normalen und pathologischen Anatomie der Hypophysis Cerebri des Menschen. *Jahrb. d. Hamb. Staatskrankenanst.* 1909, xiii, 273; Drie Fälle von Tumor hypophysen ohne Akromegalie. *Ibid.* 351.

16. Erdheim, J., and Stumme, E.: Ueber die Schwangerschaftsveränderung der Hypophyse. *Beitr. z. path. Anat. u. z. allg. Path.* 1909, lvi, 1.

17. Goetsch, E., Cushing, H., and Jacobson, C.: Carbohydrate Tolerance and the Posterior Lobe of the Hypophysis Cerebri. *Bull. Johns Hopkins Hosp.* 1911, xxii, 165.

18. Weed, L. A., Cushing, H., and Jacobson, C.: Further Studies on the Role of the Hypophysis in the Metabolism of Carbohydrates. *Bull. Johns Hopkins Hosp.* 1913, xxiv, 33.

infantilism: the animals remain undersized and the secondary sexual characteristics do not develop: there is also a tendency to hypotrichosis and to subnormal temperature. In adult dogs partial removal causes adiposity, sexual degeneration, subnormal temperature, hypotrichosis, polyuria and somnolence or restless playfulness.

Total removal of the anterior lobe causes death in sixty-eight hours with symptoms of cachexia: the consequences of stalk separation are equivalent to a total or nearly total hypophysectomy.

They also found that repeated injections of the entire gland cause a rapid loss of weight in puppies and in adult dogs; in cases of anterior lobe insufficiency injections of anterior lobe extract cause a thermic response (2 to 4 C.).

The occasional appearance of glycosuria after hypophysectomy had led these observers to further study along this line. They noticed that removal of the posterior lobe and part of the anterior lobe causes a primary fall and a subsequent rise above the normal in the assimilation limit for sugars; that removal of part of the anterior lobe, however, produces little or no alteration in the carbohydrate assimilation limit; the removal of posterior lobe alone causes no primary glycosuria, unless there is considerable traumatism of the stalk, but there is an increased sugar tolerance; this increased tolerance can be brought down to normal by giving posterior lobe extract, 1/20 gm. subcutaneously, 1/80 gm. intravenously; or 2/5 gm. by mouth. In man the normal limit for glucose by mouth is 150 gm., and for levulose 100 gm. It will be seen that in cases of posterior lobe insufficiency there is an increased sugar tolerance; such patients can take as much as 400 gm. of glucose without appearance of glycosuria.

To summarize, we may say that total removal of the gland, or total removal of the anterior lobe, causes death in two or three days, with symptoms of cachexia. Anterior lobe insufficiency in puppies caused adiposity, skeletal infantilism and failure in appearance of the secondary sexual characteristics; in adult dogs anterior lobe insufficiency causes adiposity and sexual degeneration. The symptoms of posterior lobe insufficiency are increased sugar tolerance, subnormal temperature, hypotrichosis, dry skin, low blood-pressure, adiposity and large appetite.

#### RELATION OF DIABETES INSIPIDUS TO DYSPIUITARISM

It has long been recognized that polyuria with the appearance of dextrose in the urine is a not infrequent accompaniment of acromegaly; but it is only within the last year that both experimental and clinical evidence has accumulated to prove that diabetes insipidus is probably due to disturbed secretion of the pituitary.

In 1674 Thomas Willis first recognized a distinction between two forms of diabetes, a saccharine and a non-saccharine. Claude Bernard discovered his so-called diabetic center in 1849; this point is situated in the floor of the fourth ventricle, between the centers of the pneumogastric and the auditory nerves; puncture at a point a little lower, causes simple polyuria, while puncture at a point a little higher in the frontal direction causes albuminuria.



Author's patient with hypopituitarism.

Cushing found that after certain experimental manipulations of the canine hypophysis, a postoperative polyuria was of frequent occurrence; in adults oliguria rather than diuresis follows a total extirpation; in younger animals there was diuresis. On the other hand, in a series of partial extirpations, postoperative polyuria was almost always observed. Experiments support the view that the clean-cut posterior lobe removals elicit polyuria with the greatest regularity. Schäfer found that posterior

lobe substance given by mouth increases the urinary output; the experimental polyurias have therefore been brought about either by a direct hypophyseal insult, by the injection of extracts, or by glandular implantations. An hypophyseal diuresis may also be elicited by nerve stimulation.

A review of the clinical histories included in many of the past articles on diabetes insipidus makes it clear that a large per cent. have shown symptoms found in lesions involving the base of the brain; a gummatous meningitis affecting the structures in the middle cerebral fossa being a particularly common accompaniment of the disorder. Fuchter and Frank have emphasized the surprising frequency with which primary optic atrophy, often with bitemporal hemianopsias which accompany the encephalitic polyurias, are classified as diabetes insipidus. Kohler in seven of his twenty-two cases of diabetes insipidus found an affection of the infundibulum; Oppenheim in thirty-six patients with basilar luetic meningitis observed polyuria in twelve; Kruse in thirty-four cases of bitemporal hemianopsia noticed diabetes insipidus in seven cases; Oppenheim in two cases of general cerebral symptoms with double temporal hemianopsia and diabetes insipidus found on autopsy a gumma in the region of the chiasma in one case, and a gummatous meningitis in the region of the chiasma in another; in 1882 Hagenbach found a tubercle in the infundibulum of a girl ( $4\frac{1}{2}$  years old) who had suffered a good deal from thirst and polyuria; in 1903 Rosenhaupt reported a case of diabetes insipidus in which a sarcoma of the anterior lobe of the hypophysis was found; in 1913 Frank reported a case of diabetes insipidus, due to a metastatic carcinoma of the hypophysis, and Simmond reported a case due to a gunshot wound of the hypophyseal neighborhood. The evidence, both experimental and clinical, is therefore in favor of the view that diabetes insipidus is probably a manifestation of dyspituitarism.

#### THE NERVOUS CONTROL OF PITUITARY SECRETION

Recent studies by Dandy demonstrated the presence of non-medulated fibers coursing from the carotid plexus into both lobes of the pituitary body. This histological demonstration of a sympathetic nerve supply to the gland spoke in favor of a possible nervous influence over its secretion. This discovery led Weed, Jacobson and Cushing<sup>18</sup> to study the nervous control of pituitary secretion, and to further studies on the rôle of the hypophysis in the metabolism of carbohydrates. They found, "provided there is a storage of glycogen available for discharge," that:

1. A piqure of the hypophysis in the rabbit is comparable in its glycosuric response to piqure of Bernard's so-called sugar center in the fourth ventricle.

2. Stimulation of superior cervical ganglion by faradization, or even by the manipulation necessary for its exposure, causes glycosuria in the rabbit, cat and dog.



3. Stimulation of the superior cervical ganglion, after exclusion of all possible downward impulses to the abdominal viscera by way of the vagi, cervical sympathetic trunks, or spinal cord, leads to glycosuria.

4. Stimulation of the superior cervical ganglion, after separation of all synapses of the sympathetic system by administration of nicotin, causes glycosuria.

5. Direct faradic stimulation of the hypophysis itself, by a transphenoidal operation, gives glycosuria even after preliminary transection of the spinal cord and cervical sympathetic trunks.

6. If the posterior lobe of the hypophysis has previously been removed by operation the usual stimulation of the superior cervical ganglion fails to give glycosuria.

7. Direct faradic stimulation of the hypophysis provokes glycosuria, even after transection of the spinal cord above the splanchnics.

8. A Bernard piqure will likewise cause glycosuria even after transection of the spinal cord above the splanchnics.

They came to the conclusion that stimulation of the superior cervical ganglion causes a discharge into the blood-stream of the posterior lobe secretion; this substance is presumably carried through the vascular system to the glycogen storehouses of the body, where it inaugurates glycogenolysis.

#### PHYSIOLOGICAL ACTION OF PITUITARY EXTRACT

Schäfer<sup>19</sup> and Oliver were the first to study the physiological action of pituitary extract; they experimented with the whole gland. They found that watery or salt extracts, even when boiled, raised the blood-pressure and constricted the peripheral blood-vessels. In 1898 Howell observed that the blood-pressure rise was due to posterior lobe extract only, and that when the blood-pressure was raised the pulse was slowed. In 1901 Magnus and Schäfer noticed that the pituitary extract was diuretic, and in 1906 Herring and Schäfer<sup>20</sup> observed that although posterior lobe extract constricts the arteries of the whole body, it dilates the arteries of the kidneys. Wiggers pointed out that the extract slows the heart and increases the amplitude of its contractions; he also observed that it inhibits the flow of pancreatic juice and is mydriatic. Other writers<sup>21, 22</sup> have discovered that pituitary extract causes contraction of uterine, vesical and intestinal muscles, and that it promotes the secretion of milk. Cushing pointed out that in puppies suffering from hypopituitarism, injections of anterior lobe stimulate growth and cause

19. Schäfer, E. A.: *Die Functionen des Gehirnanhangs*, Berner Universitätschriften, 1911, part B; Schäfer, E. A., and Vincent, S.: *The Physiological Effects of Extracts of the Pituitary Body*, *Jour. Physiol.*, 1899-1900, xxv, 87.

20. Schäfer and Herring, P. T.: *The Action of the Pituitary Extract Upon the Kidney*, *Phil. Tr.*, London, 1906, cxcix, 1.

21. Bell, W. B.: *The Pituitary Body and the Therapeutic Value of the Infundibular Shock, Uterine Atony and Intestinal Paresis*, *Brit. Med. Jour.*, 1909, ii, 1609.

22. Biedl, A.: *Innere Sekretion*, Berlin, 1910.

a thermic rise (2 to 4 C.), and that injections of posterior lobe lead to emaciation and reduced sugar tolerance.

#### CLINICAL MANIFESTATIONS OF DYSPIUITARISM

In man the clinical manifestations are nearly the same as those found by Cushing in dogs; the symptoms resolve themselves into those due to, (1) hypo- or hypersecretion or perversion of secretion of the gland itself; (2) those due to increased cerebral pressure; (3) those due to the local pressure of the tumor, and (4) those due to the involvement of the other ductless glands.

Deficiency of anterior lobe in children leads to infantilism; there is inhibition of skeletal development. Hypersecretion of the anterior lobe leads to gigantism in cases in which the epiphyseal centers had not yet ossified, and to acromegaly in adults; that gigantism and acromegaly are closely related is evident from the observations of Sternberg;<sup>23</sup> he found that 20 per cent. acromegalics are over 5 feet 10 inches in height, and that 40 per cent. of all giants have some signs of acromegaly. In hyperpituitarism there is hypertrophic alteration of the skin, and increase in size of the hair follicles; there is also hypertrophy of the papillae and activation of the secretory glands; so that the skin becomes greasy and moist; hypertrichosis is marked. Deficiency of posterior lobe is usually associated with adiposity and increased sugar tolerance; the temperature is usually subnormal, and the subjective chilliness and drowsiness indicate diminished metabolism. The skin is usually smooth; may even suggest edema, but does not pit; hair on the scalp may be abundant, but axillary and pubic hair may be entirely wanting; the nails are often small and do not show the crescent at their base; constipation is often obstinate and usually improves on glandular therapy; psychic disturbances are frequent and are usually due to involvement of frontal and temporal lobes. The symptoms of cerebral involvement are, change in disposition, enfeeblement of memory, disorientation and ". . . notable always is the utter lack of appreciation of, and complete indifference to, the existing condition." In hyperpituitarism, temperamental changes, wakefulness, lack of concentration and irritability are more common; in hypopituitarism mild psychoses to extreme mental derangements with epilepsy are not infrequent.

#### SYMPTOMS OF INCREASED CEREBRAL PRESSURE

These are too well known to need any detailed mention here; they are, in general, headache, general convulsions, double optic neuritis and optic atrophy, change of disposition and of mental power, vomiting, vertigo, changes in the pulse-rate and attacks of syncope; the general

23. Sternberg, M.: *Beitrag zur Kenntniss der Akromegalie*, *Ztschr. f. klin. Med.*, 1895, xxvii, 86.

symptoms occur irrespective of the location of the tumor and depend on its rapidity of growth, its vascularity and its pathological character. They vary in severity from time to time. When a tumor is growing rapidly they are very severe; if it remains stationary, they may almost disappear. Headache is the most important and constant symptom of brain tumor; it varies in intensity, but is usually severe; general convulsions are the next most frequent symptom of brain tumor; they are particularly liable to occur as an early symptom in children; vomiting is also more frequently observed in children than in adults; it usually occurs without special relation to the time of meals.

#### NEIGHBORHOOD SYMPTOMS

One of the most important local symptoms is primary optic atrophy; later there is a superimposed optic neuritis due to the growth reaching a large state. There is some distortion in the visual fields in almost all cases; bilateral defects are almost twice as common as homonymous lesions; mere tendencies toward temporal defects must be carefully looked for; particularly defects limited to color peripheries. The primary defect usually first involves the color boundaries alone, in one upper temporal quadrant; this is followed by a more or less complete temporal hemiachromatopsia; in all cases the color fields become involved first, the form fields later; the macular area is often spared for a long time, but finally becomes implicated; rarely are the two eyes affected to the same degree. Abnormal pupillary conditions are often present: a definite hemiopic pupillary response and a negative oculomotor reaction to the prism deflection of an image in the blind half of the retina may be expected when only half blindness is complete. Oculomotor implication is often present, as are also double vision, palsies and nystagmus.

Other nerves may be involved; the individual may have anosmia, tri-facial neuralgia and spasticity due to pressure on the central peduncles. Uncinate seizures are surprisingly common and the frontal lobe is not infrequently involved.

He may also have local signs in the nasopharynx, as troublesome epistaxis, intermittent discharge of mucus into the pharynx and in a few a tumor can be seen and felt in the retropharynx.

Among the most important of the local symptoms is deformation of the sella turcica; extreme hypersecretion and hyposecretion may exist with but little if any alteration in the shadow cast by the bony encasement of the gland; the sella may be well preserved, even though the tumor may be enormous and has been of long duration. There are three types of sella deformation; (1) those associated with thickening of the clinoids and dorsum epiphii; (2) those with thinning from pressure absorption of these parts, and (3) those with more or less destruction of



all outlines. Equally important are the abnormally small sellae, which accompany the primary glandular hypoplasias of the young.

#### SYMPTOMS REFERABLE TO OTHER DUCTLESS GLANDS

Although our knowledge of the internal secretions is incomplete and confused, much progress has been made in this branch of medical science in the last decade. One fact has been clearly brought out, and that is that the physiological connection of all the ductless glands is an intimate one, and that in pathological conditions of one of them all the other glands are affected.<sup>24, 25, 26, 27, 28</sup> The influence of one gland on another may be compensatory or inhibitory. The existence of a relationship between the thyroid and the hypophysis is perhaps the most satisfactorily demonstrated of all the possible interrelations of endosecretory organs. Rogowitch has found that after thyroidectomy the pituitary hypertrophies. In Basedow's disease sex functions are often affected; in myxedema there is sex depression. Parchow and Goldstein have concluded that there exists a distinct antagonism between the thyroid and the ovaries. Charrin and Jardy,<sup>29</sup> however, came to the opposite conclusion. Cooper had observed hypertrophy of the thymus in Basedow's disease. In Switzerland the offspring of goitrous mothers have both thymus and thyroids enlarged; thyroidectomy raises the assimilation limit for dextrose, showing the influence of the thyroid on the pancreas. A theory that the adrenals are related to the sex functions was proposed by Meckel (1806); in certain aborted fetuses he had noted that both the adrenals and the gonads were lacking; in animals in which sexuality is marked, the adrenals are notably large; in birds and in amphibia the gonads and the adrenals are closely associated in position. Bullock<sup>30</sup> and Sequeira have been able to find in the clinical literature twelve cases of children showing sexual precocity, who at autopsy were found to have enlarged adrenals; ten of these were females from 2 to 11 years of age. Pansini and Boneanti noticed hypertrophy of the thymus in Addison's disease. Erdheim and Stumme<sup>16</sup> found hypertrophy of the pituitary in pregnancy; the pituitary is normally held in check by secretions of the gonads.

24. Hopkins, R. G.: The Interrelation of the Organs of Internal Secretion, *Am. Jour. Med. Sc.*, 1911, cxli, 374.

25. Kidd, L. J.: The Pineal Body, *Med. Chronicle*, 1912, lvii, 154.

26. Sajous: The Internal Secretions, 1912.

27. Tandler, M.: Ueber den Einfluss der innersekretion Anteile der Geschlechtsdrüsen auf die äussere Erscheinung des Menschen, *Wien. klin. Wchnschr.*, 1910, xxiii, 459-467.

28. Vincent, S.: Internal Secretions and the Ductless Glands, London, 1912.

29. Charrin and Jardy: *Comp. rend. Acad. d. sc. Paris*, 1906, cxlii, 1442.

30. Bullock, W., and Sequeira, J. H.: On the Relation of the Suprarenal Capsules to the Sexual Organs, *Tr. Path. Soc. London*, 1905, lvi, 189.



[illegible]

Enough has been stated to substantiate the statement that every disturbance of a ductless gland is really a polyglandular disturbance, and that some of the symptoms present in disturbances of any one of the glands are probably due to the secondary involvement of the other glands.

In studying the table, it will be evident that the presence of any of the following symptoms in any case should arouse our suspicion of a disturbance in the ductless gland system. The symptoms are as follows: Dwarfism or skeletal overgrowth, adiposity or emaciation, sexual precociousness or impotence, hypertrichosis or hypotrichosis, genital hyperplasia or atrophy, mental precociousness or dulness, high or low blood-pressure, glycosuria or increased carbohydrate tolerance, asthenia, pigmentation of the skin and subnormal temperature. This table also shows that, although the same symptom may be present in disturbances of different glands, yet there are symptom-complexes which are pathognomonic and strongly point to the involvement of a particular gland.

The following symptoms present in dyspituitarism are referable to secondary involvement of the other ductless glands: Imperfectly acquired secondary sexual characteristics in cases in which the lesion antedates puberty, and of resultant amenorrhea or impotence with retrogressive sexual changes, when the malady develops after the acquirement of adolescence; pigmentation of the skin, asthenia, low blood-pressure and hypoglycemia point to adrenal involvement.

#### PATHOLOGY

Disturbances of the pituitary may be primary or secondary, functional or organic. The primary organic disturbances may be due to hyperplasia of the gland, to tumors of the gland or to tumors arising in the neighborhood of the pituitary, and which compress it and alter its secretion; such tumors usually do not cause acromegaly; any tumor of the brain or anything which prevents the secretion of this gland (e. g., hydrocephalus) from entering the third ventricle, may cause symptoms of dyspituitarism.

In 29 cases that were operated or came to autopsy, Cushing found that 23 were due to homoplastic epithelial growths and 6 were heteroplastic; of these, 1 originated from a developmental rest, 2 were teratomas, 2 infundibular cysts and 1 endothelioma. Of 60 cases of acromegaly which came to autopsy, collected by Creutzfeldt,<sup>15</sup> 8.3 per cent. were without any hypophyseal changes; 25 per cent. were sarcoma; 20 per cent. hyperplasias; 13.3 per cent. struma; 20 per cent. adenoma; 1.6 per cent. glioma; 6.6 per cent. no definite diagnosis made. In 55 cases of tumor of the hypophysis, without acromegaly, he found sarcoma in 27.27 per cent.; hyperplasia in 9.09 per cent.; struma in 5.45 per cent.; ade-

noma in 18.18 per cent.; *Platten epitheltumoren*, 34.54 per cent.; teratoma, 1.8 per cent.; lipoma, 1.8 per cent., and metastatic, 1.8 per cent.

#### CLINICAL TYPES

One of the earliest types to be recognized is acromegaly.<sup>3</sup> This type is too well known to need any detailed description. Closely associated with this type are the cases of gigantism;<sup>31</sup> they are both due to hypersecretion of the anterior lobe; gigantism occurs in cases in which the epiphyseal centers had not yet ossified; whereas, acromegaly usually occurs in adults; still cases of acromegaly have been reported in children by Antonini and Marzocchi, de Cyon,<sup>32</sup> Rake, Salle and others. The most notable symptoms of acromegaly are skeletal overgrowth, *main en large*, phalangeal alteration, mandibular prognathism, spacing of teeth, rounding of shoulders, sternoclavicular enlargement, peculiar cranial configuration and hypertrichosis.

#### TYPE FRÖHLICH

To this type<sup>6</sup> belong those cases which have neighborhood symptoms of tumor of the hypophysis, without any evidences of acromegaly; these cases have a peculiar adiposity; with a feminine type of distribution of the fat when it occurs in males; there is aplasia of the genitals, hypotrichosis, subnormal temperature, undersized stature, psychoses of varying nature and increased carbohydrate tolerance. These cases are due to hyposecretion of the posterior lobe. Such cases in children have been reported by Fröhlich, Babinski, Hochwart, Uhlthoff, Cagnetto,<sup>33</sup> Erdheim, Israel, Woolcombe, Creutzfeldt, Cushing and others.

#### TYPES BURNIER

In 1912 Burnier<sup>8</sup> collected a group of cases from the literature and added one of his own cases, which in addition to local signs of hypophyseal tumor and signs of posterior lobe insufficiency, showed marked dwarfism. These cases are due to hyposecretion of both lobes. The most important symptoms of this type are optic nerve atrophy (almost invariably present), adiposity, dwarfism and atrophy of external and internal genitals. Such cases have been recorded by Burnier, Kon, Benda, Hutchinson, Heuter, Bartels, Nazair, Zöllner, Mixer and Quackeboss and others.

#### TYPE CUSHING

It is Cushing who pointed out that a pituitary may be hypersecreting at one time and hyposecreting at another; and that in fact all cases of

31. Launois, P. E., and Roy, P.: *Etude biologique sur les géante*, Paris, 1904.

32. Cyon: *Prog. méd.*, 1898.

33. Cagnetto: *Virchow's Arch. f. path. Anat.*, 1904.

hyperpituitarism show evidences of hypopituitarism as the disease progresses. It is he also who made the observation that one lobe may be hypersecreting and the other lobe hyposecreting at the same time; and thus we may have a variety of mixed types. He especially called attention to cases of skeletal overgrowth associated with adiposity and sexual infantilism without acromegaly.

#### DIAGNOSIS

Diagnosis of acromegaly and gigantism is simple; the Roentgen rays, however, are of great aid. They may show an enlarged sella turcica, or they may show enlargement, broadening and tufting of the phalanges. In posterior lobe insufficiency, the estimation of the sugar tolerance is of importance. We must always suspect posterior lobe insufficiency in individuals who can take more than 150 gm. glucose and 100 gm. levulose by mouth without glycosuria. In some cases of anterior lobe hyposecretion there is a thermic response when they receive an injection of anterior lobe extract. The symptom-complex of skeletal overgrowth or dwarfism, adiposity, genital atrophy, optic nerve atrophy, deformation of sella and increased carbohydrate tolerance are absolutely pathognomonic of dyspituitarism.

#### TREATMENT

Treatment may be medical, surgical or both; surgical intervention is indicated to relieve general central pressure; to relieve neighborhood symptoms and to implant pituitary gland in cases of hyposecretion. To relieve general cerebral pressure symptoms a subtemporal decompression is indicated; for the neighborhood symptoms, fragmentary extirpation of the tumor or removal of the sellar floor and opening of the capsule are the operations of choice in the absence of pressure symptoms, but when headaches are very severe a sellar decompression should be advised. The medical treatment consists in the application of radium after operation and the administration of whole gland extract by mouth or hypodermically, the dose varying in each case, depending on the amount of posterior lobe insufficiency.

Alex. K., 12 years old, was brought to the Vanderbilt clinic (Pediatric section), by his mother, April 27, 1912. The mother's chief concern was that her son's genitals were very much undeveloped; she also stated that he suffered a great deal from headaches, vertigo, double vision and vomiting, and that he always felt cold.

Family history was negative. A brother of the patient, who had also been treated at the clinic two years previously, was a Mongolian idiot and had died of pneumonia. The birth of the patient was normal; he was breast fed for nine months; he had pneumonia at 5 months and measles at 1 year; suppurative adenitis at 2 years; no other acute illness; for the last two or three years the patient had been complaining of headaches, double vision, vertigo and vomiting; the vomiting was regardless of the nature of food or time of feeding. He was always cold and suffered a good deal from constipation.



Physical examination revealed a very well nourished boy; weight 93½ pounds (normal weight for boy of 12 years is 81 pounds); height 53 inches (that is 4 inches undersized for his age); facies was somewhat peculiar and the expression anxious; slight exophthalmos was present; no enlargement of the thyroid could be made out; chest and abdomen negative; the adiposity was of a feminine type of distribution; the fat folds over the hips, knees and feet were quite marked; the genitals were hypoplastic; there were no axillary nor pubic hair; the fingers were of a peculiar tapering kind; there was a fine tremor of the fingers present; the pulse was 84 to the minute; temperature 97.8 F.; examination of the eyes revealed a bitemporal hemianopsia; mentality was normal; Roentgen ray examination of the hands showed nothing abnormal; that of the head showed slight enlargement of the sella turcica.

May 14, 1912, the patient was given 250 gm. of glucose on an empty stomach, and all subsequent specimens of urine were collected; none showed any sugar; this was repeated three times with the same result; levulose the patient could not tolerate in any form; it was invariably vomited. The patient was given 10 grains of pituitary extract (whole gland) three times a day. The urine was constantly examined while the patient was under treatment and no glycosuria appeared; the temperature, which was subnormal before treatment; never ranged lower than 99 F. after treatment was instituted; the constipation was also much relieved; the pulse ranged from 85 to 100. Under treatment the patient lost 10 pounds in two months; treatment had no effect on the headaches, vertigo or vomiting; a sellar decompression was suggested, but was refused and the patient stopped coming to the clinic.

The presence of genital hypoplasia, hypotrichosis, adiposis, skeletal undergrowth, with symptoms of cerebral pressure and an enlarged sella turcica, led us to conclude that we were dealing with a case of hyposecretion of both lobes (type Fröhlich), probably due to a tumorous growth. The presence of slight exophthalmos, tachycardia and tremor suggest the presence of hyperthyroidism, which is secondary and probably of a compensatory nature, as the thyroid and the pituitary are synergic.

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# A STUDY OF THE WASSERMANN REACTION IN ONE HUNDRED INFANTS \*

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In an article entitled "The Wassermann Reaction in Children and Infants," Churchill<sup>1</sup> states that a positive serum reaction was found in thirty-nine of 101 children examined. The cases were taken "mostly at random" from a large hospital for children. There was a family or past history of syphilis, or signs of the disease, together with a positive serum reaction in twenty-nine of these cases. In the ten other cases, the serum reaction was positive without a history of or evidences suggestive of syphilitic infection. The technic used in some of the cases was that recommended by Wassermann, but in the majority the Noguchi modification was employed. Churchill was surprised to find so large a number of positive serum reactions in children apparently free from syphilis, but he wisely suggested that further studies were necessary before valid conclusions as to the incidence of latent hereditary syphilis could be drawn.

## AUTHORS' INVESTIGATION

In this investigation the sera from 101 infants, irrespective of the reason for which they were in the hospital, were tested. The technic employed was that advocated by Wassermann, and in forty-three instances this was supplemented by tests made according to the method of Noguchi. The blood was procured by means of the suction apparatus described by Blackfan.<sup>2</sup> The collection, from infants, of blood for the Wassermann test has always been attended with difficulty, but by the use of this method a sufficient quantity for both tests was easily obtained. Effort was made to collect all data that might aid in establishing a diagnosis of hereditary syphilis.

*Group I.*—In this group there were 68 infants from a large foundling hospital. The youngest child was 5 days old, and the oldest was 29 months; 20 were under 6 months, 24 under 12 months, 16 under 24 months and 8 between 24 and 29 months.

\* Submitted for publication May, 1913.

1. Churchill, F. S.: *JOUR. DIS. CHILD.*, 1912, iii, 363.

2. Blackfan, K. D.: *JOUR. DIS. CHILD.*, 1912, iv, 33.

The *family history* could not be obtained in the majority of cases. The *past history* and *physical examination* failed to show in a single instance any evidences of hereditary syphilis. Of the 68 infants tested, 44 were normal and well nourished, 19 were slightly rachitic, 2 had Hirschsprung's disease, 1 had icterus neonatorum, 1 had tetany and 1 had meningitis (probably tuberculous).

*Group II.*—There were 33 infants in this group, from the wards and the out-patient department of the St. Louis Children's Hospital. The youngest child was 2 weeks of age and the oldest was 30 months; 9 were under 6 months, 10 under 12 months, 12 under 24 months and 2 between 24 and 30 months.

The *family history* was known in all of the cases except one, an illegitimate baby 2 weeks old. It had no bearing on the question at hand in 29. In the remaining 3 cases, there were certain facts suggestive of syphilis. In Case 32, the mother had had one miscarriage and in Case 31, the mother had had two miscarriages. In Case 33, to which reference will be made later, besides the family history, the past history and physical examination were also suggestive of syphilis. The *past history* and *physical examination* of 32 infants in this group presented no evidences of syphilis. The cases studied included children with:

Nutritional diseases .....	18
Severe burn .....	1
Bronchitis .....	1
Eczema .....	1
Pyelocystitis .....	1
Pneumonia .....	3
Idiocy, Mongolian .....	1
Tuberculosis, pulmonary .....	1
Spastic Paraplegia .....	2
Normal .....	4

#### RESULTS OF THE SEROLOGICAL TESTS

Of the 68 infants comprising Group I, the Wassermann test showed *no fixation* of complement in 66. These 66 cases do not require further consideration inasmuch as the clinical findings failed to show any evidence of syphilis.

Of the remaining 2 infants, there was slight fixation of complement in the serum from one by both the Noguchi and the Wassermann method. This infant (No. 68), 29 months old, was well nourished and there was no reason from the past history or physical examination, to suspect hereditary syphilis. The serum was tested at three different times, and each test gave slight fixation. As there were no clinical evidences of syphilis and as the fixation test at no time was definitely positive, a diagnosis of hereditary syphilis could not be made. The case of the other infant (No. 67) is of interest because no clinical evidences of latent hereditary syphilis were found and the serum caused complete fixation of



complement. This child, 28 months old, was well developed and well nourished, and had been in the institution since birth. The blood was tested repeatedly, and each time showed complete fixation by both the Noguchi and the Wassermann methods. In view of our present knowledge regarding the specificity of the Wassermann reaction, this establishes the case as one of hereditary syphilis in spite of the lack of confirmatory clinical signs.

Of the 33 infants composing Group II, the Wassermann test showed *no fixation* of complement in 32, and *complete fixation* of complement in 1.

The infant (No. 33) whose serum showed complete fixation of complement presented signs of syphilis when admitted to the hospital. The mother had had one miscarriage and one still-birth. The baby had had, a few weeks after birth, the snuffles and a desquamation of the skin from the palms of the hands and the soles of the feet. On admission at 6 months of age, the patient, who was undernourished and poorly developed, weighed  $7\frac{1}{2}$  pounds. The spleen was enlarged and the superficial lymph-nodes were palpable. This, without question, was a case of hereditary syphilis.

## GROUP I

Case No.	Family History	Past History	Phys. Ex.	Wassermann
1-66	Not known	Negative	Negative	No fixation
68	Negative	Negative	Negative	Partial fixation
67	Negative	Negative	Negative	Complete fixation

## GROUP II

Case No.	Family History	Past History	Phys. Ex.	Wassermann
1-30	Negative	Negative	Negative	No fixation
31	2 miscarriages	Negative	Negative	No fixation
32	1 miscarriage	Negative	Negative	No fixation
33	1 miscarriage	Snuffles	Palpable	Complete fixation
	1 stillbirth	Desquamation	Spleen	

To recapitulate: In Group I there were 68 children, none of whom gave, on investigation of their family or past history or by physical examination, any evidence of hereditary syphilis. The Wassermann reaction was negative in 66, doubtful in 1 and positive in 1. The Noguchi modification was made in 43 of the cases in this group, and verified the results of the Wassermann test; i. e., 41 sera were negative, 1 was doubtful and 1 was positive.

In Group II no clinical evidences of hereditary syphilis were found in 30 infants. In 2 infants the family history was suggestive. In 1 infant, the family and past history and the physical examination were suggestive of syphilis. The Wassermann reaction was negative in 32 of the infants and positive in 1 infant.

These findings are not surprising. They confirm the already established fact that in the majority of patients in which the family and past history and the physical examination are negative, the serum reaction is



likewise negative. In the same manner a positive reaction in the serum of a patient with signs of the infection, as is shown by Case 33, is to be expected.

That a child without clinical evidences of syphilis, but whose serum gives a positive Wassermann reaction, may still be syphilitic, is not a new disclosure, for it has long been recognized that hereditary syphilis may remain latent for an undetermined period, and become manifest at a later date. Case 67 is such an instance and emphasizes the great value of the Wassermann test.

The significance of a so-called partial or weak reaction, like that obtained with the serum from Case 68, is not perfectly clear, and judgment as to the nature of the case should be deferred. Observation of the patient and frequent repetitions of the test, must teach the meaning of this type of reaction as an aid to the diagnosis of hereditary syphilis.

Regarding the incidence of latent hereditary syphilis as determined by means of the complement fixation test, larger series of cases must be studied and much more information obtained before definite conclusions can be drawn. The finding by us of one case of latent hereditary syphilis is at variance with Churchill's results, but that this difference is more apparent than real, is evident from an analysis of the cases in his Group V. In this group of his are included children without definite signs of syphilis and without a suggestive history, but with a positive serum reaction. He states that "there is no ground, except a positive serum reaction, for regarding four in this group (Nos. 1, 12, 20 and 31) as cases of syphilis." It seems to us that these should be regarded and classified as cases of latent hereditary syphilis. The positive serum reaction can be explained only on this basis, and a failure to accept this explanation must be taken as an admission of doubt as to the specificity of the complement fixation test, or as an acknowledgment of some error in technic. It would be interesting to know the future history and clinical course of these patients.

The results of this series, in which only two cases gave a positive serum reaction, are strikingly low as compared with the thirty-nine positive cases found by Churchill and consequently do not confirm his observations regarding the frequency of hereditary syphilis among hospital children. Several factors concerning the complement fixation test should be kept in mind as a possible explanation for such a wide variation, viz., the hypersensitiveness of the Noguchi as compared to the Wassermann technic; the personal element present in the interpretation of the reaction and the possibility of error in technic.

These two investigations show conclusively that small series from different sources give widely divergent results, and that further studies of larger series of cases are necessary in order to determine the prevalence of hereditary syphilis among hospital children.

# THE WASSERMANN REACTION IN HEREDITARY SYPHILIS, IN CONGENITAL DEFORMITIES AND IN VARIOUS OTHER CONDITIONS IN INFANCY

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There is probably no modern means of diagnosis of greater importance than the Wassermann reaction. This not only enables one to be certain of the existence of syphilis in many doubtful conditions, but also to exclude syphilis in many cases where formerly it was suspected. It is the consensus of opinion at present that latent as well as active syphilis gives a positive response to this test. It is also the general belief that children who react positively should receive the benefit of antisyphilitic treatment.

Like all laboratory reactions, the Wassermann test is not infallible. Positive reactions may be obtained in certain cases of scarlet fever and in infection with trypanosomes; but neither of these conditions is very likely to be confused with syphilis. Negative reactions may be met with in syphilitic cases as a result of treatment, whether by mercury or salvarsan, and occasionally in other cases for unexplained reasons. With proper technic the errors are chiefly on the negative side, but they are not numerous. Errors due to faulty technic must also be taken into account. These are much more common and are almost always on the positive side, so that the children tested are pronounced syphilitic when they are not so. It is absolutely essential that reagents used should be right; that the antigen be good and well tested; and that sheep or human corpuscles be fresh, preferably less than twenty-four hours old, and properly washed. A mistake in technic is the probable explanation of the large percentage of positive reactions obtained in children by some writers. One person with such an experience has, indeed, recently written to me raising the question whether the Wassermann test can be relied on in infants. It had been used on those who were to be placed out for adoption and the number of positive reactions obtained was most disturbing. Under such circumstances doubt should be cast on the manner in which the test was made, rather than on the value of the test itself.

It was to answer the question as to the frequency of active or latent syphilis in the ordinary run of hospital infants as well as in some special

conditions, particularly congenital deformities, that a series of observations has been carried on in the Babies' Hospital during the past year and a half.

The Noguchi modification of the Wassermann test has been employed in all of our patients. This has the great advantage, in the case of infants, of requiring much less blood (only  $\frac{1}{2}$  of a c.c.) than the Wassermann test. All of these tests, with the exception of those in the last group of seventeen children examined, have been made at the Rockefeller Institute by one of Dr. Noguchi's assistants and under his supervision. I think we may, therefore, be certain as to the reliability of the technic and the accuracy of the observations.

During the period mentioned, 34 cases of hereditary syphilis were admitted for treatment. In 31 of these, blood tests were made, and 30 gave a positive reaction. The single case not responding was in an infant 5 months old, in whom there was a typical history of syphilis, but the child had been treated regularly with inunctions of mercury for a period of three months before.

Previous treatment with mercury does not seem to affect the reaction unless it has been continued for a considerable time and with regularity. For of the 30 patients giving positive reactions, 9 had been treated with mercury as follows: One an infant 6 months old, for two weeks; two sisters of  $4\frac{1}{2}$  and 22 months, irregular treatment with inunctions since birth; one infant of 6 weeks, inunctions since it was 4 days old; one child of  $2\frac{1}{2}$  years, inunctions irregularly from birth; one infant of 7 months, inunctions and mercury internally for one week; one infant of 21 months, irregular inunctions and potassium iodid almost from birth; one child of  $2\frac{1}{2}$  years, irregular inunctions from birth. If we adopt the ordinarily accepted view that a positive Wassermann reaction is an indication that the patient is not cured and still requires treatment, it will be evident from the cases just cited how incomplete and how uncertain is the cure of syphilis effected by mercury and potassium iodid.

Of children who were not regarded clinically as syphilitic, 178 were studied. While this number is not large, it should be remembered that these cases were selected from about 1,800 hospital admissions, and that they include, in the first place, nearly every child in whom even a slight suspicion of syphilis existed. Besides, a considerable number of infants suffering from marasmus or malnutrition without selection were examined, all cases with congenital malformations, and a miscellaneous group of various acute and chronic diseases also unselected. Of the 178 tested, 167 gave negative reactions, and 11 positive reactions. The ages of the children were as follows:



	Positive	Negative	Total
Under 6 months.....	5	85	90
6 to 12 months.....	2	33	35
1 to 2 years.....	3	33	36
Over 2 years.....	1	16	17

*Positive Cases.*—Of eleven children showing no definite clinical evidence of syphilis, but giving a positive reaction, five died and came to autopsy. Four of these showed perisplenitis and perihepatitis of sufficient degree to warrant a pathological diagnosis of syphilis. Three of these were marasmus infants. In one of them there could be discovered no family history suggesting syphilis; in one the mother had had three previous miscarriages; in a third there was one previous miscarriage, but otherwise a negative family history; in a fourth, a child dying of acute gastro-intestinal intoxication, the parents gave a definite history of syphilis, and the child had general glandular enlargements. In only one case giving a positive reaction which came to autopsy, did the family history, the examination of the patient, or post mortem findings give no suggestion of syphilis.

Of the six positive cases which terminated in recovery, two were in rachitic infants with moderate enlargement of the liver and spleen; one was a child with spastic diplegia, whose mother gave a positive reaction; one was a case of sclerema, with moderate enlargement of liver and spleen, but with a negative family history; one was a cretin with a negative family history, and one, a child admitted for convulsions of unknown origin. The positive reaction in the infant last mentioned led to tests of both parents, but neither responded. There was nothing in this patient's symptoms to suggest syphilis.

We have, therefore, in this group of eleven cases, only three in which no evidence of syphilis could be found, either in the family history, the clinical symptoms or the pathological findings. In the remaining eight positive cases, the evidence of syphilis was practically conclusive in five; in the other three cases, rickets and enlarged liver and spleen were present.

*Negative Cases.*—One hundred sixty-seven children gave a negative reaction. In this group, twelve came to autopsy and in none of them were any lesions present suggestive of syphilis. The largest single group were fifty-six infants with malformations or congenital deformities. Inasmuch as syphilis has been thought to be an etiological factor in certain of these conditions they were made a subject of special study. These cases were as follows:

Spina-bifida .....	10	Defective cerebral development...	6
Mongolian idiocy .....	8	Cystic kidney .....	1
Spastic diplegia .....	6	Hygroma of the neck.....	1



Congenital cardiac disease.....	6	Congenital obliteration of the	
Hare-lip and cleft palate.....	5	bile ducts .....	1
Hydrocephalus .....	5	Amaurotic family idiocy.....	1
Exstrophy of the bladder.....	1	Clubfeet and hands.....	1
Microcephalus .....	4	Total .....	56

The remaining cases were divided as follows:

Marasmus and malnutrition....	57	Rachitis .....	3
Acute pneumonia.....	16	Tumor of the brain.....	2
Empyema .....	5	Chorea .....	2
Tuberculosis .....	7	Duodenal ulcer .....	3

And one each of the following conditions: Pemphigus neonatorum, meningeal hemorrhage, scurvy, leukemia, diabetes, encephalitis, poliomyelitis, papilloma of the larynx, chronic nephritis, eczema, basilar meningitis, acute arthritis, hernia, convulsions, ulcerative stomatitis, hydrocephalus. Total, 111.

From these observations it would appear that syphilis does not play an important part in the production of the common congenital deformities, since in not a single one of fifty-six consecutive cases studied was a positive reaction found. Again, it has been assumed that syphilis was exceedingly common in the marasmus type of infant admitted to a hospital. I remember many years ago while visiting the marasmus wards of the Blockley Hospital in Philadelphia, asking of the attending physician, who was showing me through the institution, what he did for this class of patients. "We give them all mercury and the iodids; they are all syphilitic," was his reply.

The presence in marasmus patients of enlargement of the liver and spleen and superficial lymph-nodes is not sufficient to warrant the diagnosis of probable syphilis. This is so often assumed that we have made the size of the spleen and liver a subject of special study in all patients examined. In the 167 negative cases the liver was much enlarged in 12 and palpable in 39 others. In the patients showing much enlargement of the spleen, the liver was almost invariably enlarged also, 7 of the cases showing much hepatic enlargement, and 8 of those showing splenic enlargement were rachitic.

There was general enlargement of the superficial lymph-nodes, sufficient to be noted, in fifty-two cases, or 33 per cent., and in twenty of these the swelling was considerable. It is evident, then, that mere swelling of the liver and spleen even when associated is not to be regarded as a very important sign suggestive of syphilis in infants suffering from malnutrition. Both are much more likely to be seen with rickets than with syphilis. Moreover, general swelling of the superficial lymph-nodes, whether occurring alone or with swelling of the liver and spleen, has no special significance. The only glandular swellings that do suggest syphilis are those of the epitrochlears when they occur without any peripheral lesion to explain it.

## CONCLUSIONS

Cases of hereditary syphilis almost invariably respond positively to the Wassermann test, even when previously treated by mercury, unless the treatment has been very thorough and protracted.

After the use of salvarsan it has been my experience that it disappears much more regularly and earlier, but even then in most cases only after repeated injections.

Of 178 tests made in hospital patients showing no definite signs of syphilis, positive reactions were obtained in but eleven and five of these were shown on fuller investigation or subsequent findings to be pretty clearly syphilitic. Two of the remaining six were doubtfully so.

The great portion of congenital deformities have no relation to syphilis, since not a single positive reaction was obtained in fifty-six consecutive cases.

Of sixty-two patients suffering from malnutrition or marasmus, only five gave a positive reaction, and are included in the group above mentioned. Of the remaining fifty-seven, nearly one-third had very considerable enlargement of the spleen or liver, or both. Since the cases examined were selected from a much larger number, as those most likely to be syphilitic, we cannot regard syphilis as a common cause of marasmus, certainly in the patients admitted to the Babies' Hospital. Since the error, when one exists, is almost invariably on the positive side, the technic of those who find a very large proportion of positive reactions among marasmus patients in institutions is open to suspicion.

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## THE LUETIN REACTION IN INFANCY \*

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Stimulated by the discovery of the cutaneous skin test for tuberculosis, numerous observers, notably Wolff-Eisner, Neisser and Meirowsky, attempted to obtain a similar reaction specific for syphilis. These investigators used syphilitic extracts of liver, but their results on the whole were conflicting, owing to the fact that they obtained reactions with normal liver extracts, as well as those with extracts from syphilitic livers. This peculiar reaction toward normal liver extracts in syphilitic individuals, was described by Neisser as the state of "*Umstimmung*," or allergic reaction. It was not till 1911 that Noguchi, using pure cultures of numerous strains of the *pallida* grown on solid media and then ground in a mortar, produced the substance known as *luetin*. By this process Noguchi claimed that not only spirochetes of different ages, but, in addition, the products of their metabolic processes, were obtained, and these factors he considered important in order to produce a state or condition of allergy or sensitization in persons supposed to be syphilitic.

The luetin as prepared by Noguchi is preserved in 0.5 per cent. trikresol. A syringe graduated in 0.5 c.c. is necessary. The skin is prepared as for the tuberculin skin test. The site chosen for injection is preferably the outer side of the upper arm, and the control, which consists of ground agar preserved in 0.5 per cent. trikresol, is injected into the opposite arm. The injection in each instance should be made intradermally, .05 c.c. being used. If the injection has been properly made the epidermis is raised to form a pale circle which disappears within a half hour; this happens with both the luetin and control.

With the injection used for control there is seen within eighteen to twenty-four hours a slight erythema around the point of puncture which disappears within two days. Where the luetin is injected there occurs within one to two days a red indurated papule, which slowly increases during the following four to five days, and then subsides, leaving a brown desquamating induration. This slowly disappears in the course of a few weeks. Occasionally, the indurated papule may go on to pustule formation.

Noguchi describes a torpid form in which nothing is seen till two or possibly three weeks after the injection, but which thereafter runs its usual course. This was not observed in our series of tests. With nearly

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\* From the service of L. Emmett Holt, M.D., The Babies' Hospital, New York.

every infant there was some variation in the degree of reaction, both as regards erythema and induration. The pustule, when present, was not larger than 2 or 3 millimeters in diameter. In many syphilitic infants the skin is very much thickened and indurated and in such cases the reaction is very difficult to interpret. This is also the case when the child is very anemic. It is in just such cases that faulty conclusions are apt to be drawn and it seems that in these instances the extent of the induration is of more value for diagnosis than the presence of the erythema, which may be very slight.

In all, 134 tests have been made at the Babies' Hospital. Thirty-four were in patients with hereditary syphilis, and 100 in controls. Of the syphilitic infants all but four gave a positive luetin reaction. In the 100 controls, ninety-six were definitely negative and four gave a doubtful reaction. All of the negative cases were also negative to the Wassermann test. In all the cases regarded as syphilitic the diagnosis was confirmed by the Wassermann reaction and the clinical history.

The reactions according to age were as follows:

	Positive Reaction	Negative Reaction
1 to 3 months .....	12	4
3 to 6 months .....	8	—
6 to 12 months .....	6	—
1 to 4 years .....	4	—
	30	4

Of the syphilitic patients with a negative luetin reaction, all four were cases of severe infections and either the hemoglobin was very low or the skin much thickened so that one could not be certain of a positive reaction. Of the thirty positive luetin cases, fifteen showed small pustules; the other fifteen reacted in the form of a definite inflammatory papule. In addition it was observed that the more energetic the treatment the more distinct was the reaction. Especially was this the case after salvarsan injections.

The influence of treatment on the luetin reaction was as follows:

	No. of Cases	Positive Reaction
A. Salvarsan only .....	16	16
B. Mercury and salvarsan.....	3	3
C. Mercury only .....	5	5
D. No treatment .....	10	6

The cases used for control embrace a wide variety of pathological conditions. They were as follows:

	Cases
Marasmus .....	34
Pneumonia .....	22
Empyema .....	4
Tetany .....	3
Gastro-Enteritis .....	3



Two cases of each of the following: Spastic diplegia, cretinism, mongolian idiocy, eczema, rachitis, hernia, congenital heart disease, and tuberculous peritonitis. Total, 16.

One case of each of the following: Sclerema, bronchitis, retropharyngeal abscess, pemphigus neonatorum, scarlet fever, tuberculous meningitis, adenitis, Still's disease, nevus, cleft-palate, hare-lip, hygroma, mental deficiency, and tuberculous adenitis. Total, 14.

In none of these cases was a positive reaction obtained with the luetin test. Four other children gave a suspicious or doubtful reaction, but in only one was a positive Wassermann reaction obtained. This was a child 14 months of age, suffering from von Jaksch's anemia, who gave no clinical evidence of syphilis.

There were fourteen infants in whom the test was repeated after injections of salvarsan; of these, eight became negative during an average period of five months after the first injection of salvarsan. In each instance the Wassermann reaction corresponded with the luetin test, i e., it became negative at or about the same time. In the remaining six positive cases the reaction was present at the time of the last test made, which averaged three and a half months after the first injection of salvarsan. In this group also the Wassermann corresponded with the luetin test.

#### CONCLUSIONS

1. These observations indicate that the luetin cutaneous reaction is a valuable addition to the means of diagnosis of hereditary syphilis.

2. In the tests made in the hospital the results have corresponded closely with the clinical symptoms and the Wassermann reaction.

3. The luetin test has the obvious advantage that it can be readily applied anywhere by anyone and the technic is comparatively simple.

4. The interpretation of the reaction requires considerable experience, but with this the number of doubtful reactions is small.

## RESULTS WITH SALVARSAN IN HEREDITARY SYPHILIS

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During the period extending from November, 1911, to January, 1913, there were treated in the Babies' Hospital thirty-four cases of hereditary syphilis by salvarsan alone. In all this series of cases the injections were given intravenously at the bend of the elbow. The technic was as follows: General anesthesia; a careful dissection of the vein and injection through a fine glass cannula which was substituted for the needle. In other respects the procedure followed was that usually observed in salvarsan injections.

This method of injection was found rather troublesome, tedious and somewhat difficult owing to the small size and fragile condition of the veins of these patients. The difficulties were, however, in a measure overcome with experience, and the time consumed in the operation was usually from fifteen to twenty minutes. In our later cases this method of injection was abandoned and the injections made with a needle directly into the external jugular vein. We used a 5 c.c. glass Luer syringe with a No. 22 gauge needle 1.5 cm. in length. The patient's arms were secured in a sheet and the head hyperextended and rotated to the side of the vein not used. The crying of the child caused the vein to stand out more prominently and facilitated the introduction of the needle. This plan of procedure was found quite satisfactory, except in very fat children. In them it is almost impossible to reach the vein without dissection. This has led us to try in recent cases the veins of the scalp, which have been found to be much more satisfactory than either of the preceding. Either the posterior auricular or one of the branches of the temporal vein may be used. These veins are readily entered on account of their bony and fibrous surroundings. The child is prepared as when the external jugular is to be used. Crying of the child and hyperextension of the head, make the vein more prominent. This method of injection has been found to have so many advantages over the others used that latterly it has been the only one employed.

The dose employed for infants up to 8 months of age was .05 gm. of salvarsan or 0.075 gm. of neosalvarsan; above this age, from .10 to .20 gm. of salvarsan or .15 and .30 gm. of neosalvarsan, according to the

age of the child, was given. A local reaction followed in but a single case, and in this there was only a slight induration, which persisted for a few days. In no instance were any untoward general symptoms observed as a consequence of the injection. The children usually were kept in the hospital for three or four days after the injections were made and were returned for subsequent treatment.

The patients injected were taken without selection, and they include all the patients with hereditary syphilis admitted during the period mentioned. No matter how hopeless the condition when the infant was brought to the hospital, it was given the benefit of the treatment in order to test the value of salvarsan in desperate cases.

*Condition on Admission.*—Only two of the thirty-four children were considered in good condition at the time of admission; twenty-two were in fair condition; six in very poor condition and four were in such a wretched state that they were regarded as hopeless, and lived less than three days. The weights, even better than this description, will give an idea of the condition of the children: Fourteen weighed 8 pounds or less; ten weighed between 8 and 10 pounds; and only ten were over 10 pounds.

Nineteen of the patients were under three months of age, four being under 1 month; eight were between 3 and 6 months; seven over 6 months, five of these being over 1 year old.

Only six of the children were exclusively breast-fed; four were partly nursed and partly fed; and twenty-four were bottle-fed entirely. This not only explains their bad condition, but also was an important factor in determining the results of treatment. With respect to severity of symptoms, seventeen were classed as severe and seventeen as mild infections.

Complete blood examinations were made in all the cases, the usual changes found being those of a secondary anemia of moderate degree. It is, however, of interest to note the marked eosinophilia present in three of the patients; the highest noted was 23 per cent. of the white cells.

Spirochetes were sought in twenty-one of the cases and were demonstrated in all but one of these. The stain employed was the Chin-Chin Pearly India ink, which has been found entirely reliable and simpler than the more commonly used Geimsa stain.

Wassermann tests were made in thirty-one children; all but one of these gave a positive reaction, this being a child who had been energetically treated with mercurial inunctions for a period of three months.

As generally administered, the dose of salvarsan we have used, .05 gm., is dissolved in 25 c.c. of distilled water. This amount is too large to be injected into one of the veins of the scalp or the jugular. By



experience we have found that 5 c.c. of water was sufficient and no irritation followed injections in this degree of concentration.

*Repetition of Doses.*—The plan followed has been a somewhat tentative one; we have been in the habit of giving the second dose two weeks after the first, and subsequent doses at intervals of from one to two months, being influenced by the result of the Wassermann test.

*Results.*—In estimating the effects of salvarsan in hereditary syphilis we have considered its influence on the spirochetes, the Wassermann reaction, the rash and other syphilitic symptoms and the patient's general condition. The examinations for spirochetes were made in most cases every second day, in a few cases daily, and in none at longer intervals than three days. The spirochetes disappeared on the average in four and a half days after the first injection; the shortest time was one day in one case and two days in another case. The longest time they persisted was thirteen days in a single case.

Circumstances did not permit our having the Wassermann reaction taken oftener than once a month, and in some of the patients only once in two months. In sixteen patients in whom frequent Wassermann tests were made, the average time of disappearance of the reaction was three and one-half months; the earliest being two months and the latest nine and a half months; the latter in a patient who had received four injections. In two patients positive reactions were obtained, one in two and the other in two and a half months subsequent to the negative reaction. One of these patients remained positive in spite of two later injections, and the other after a single injection. In five patients who were observed on the average for a period of three and one-half months, the positive reaction never disappeared, although one patient had four injections and four had two injections. The status of the cases as regards the Wassermann reaction at the time of latest report was as follows: Of thirty-four patients treated, seventeen had died and one was lost sight of; of the sixteen living, six were positive and ten were negative, the latter having been under observation for an average of ten months.

The effect of salvarsan is most strikingly seen on the cutaneous lesions. Patients admitted with profuse eruptions and moist lesions, especially of the face, often showed marked improvement in twenty-four hours, and within a week the skin, as a rule, was almost normal, only the pigmentation remaining.

The following case with the illustrations attached is a good example of what was often seen.

#### CASE REPORTS

CASE 1.—F. G., aged 1 month, admitted with a severe infection. The central part of face, mouth, nose, forehead and chin were covered with an intense maculopapular eruption and about the mouth were many crusts with moisture and



hemorrhage. The lower extremities were covered with a maculo-papular eruption as shown in the illustration (Fig. 1). The blood examination showed an eosinophilia of 21 per cent. The patient was given .05 gm. salvarsan. In twenty-four hours an improvement in the cutaneous lesions was evident, the eruption

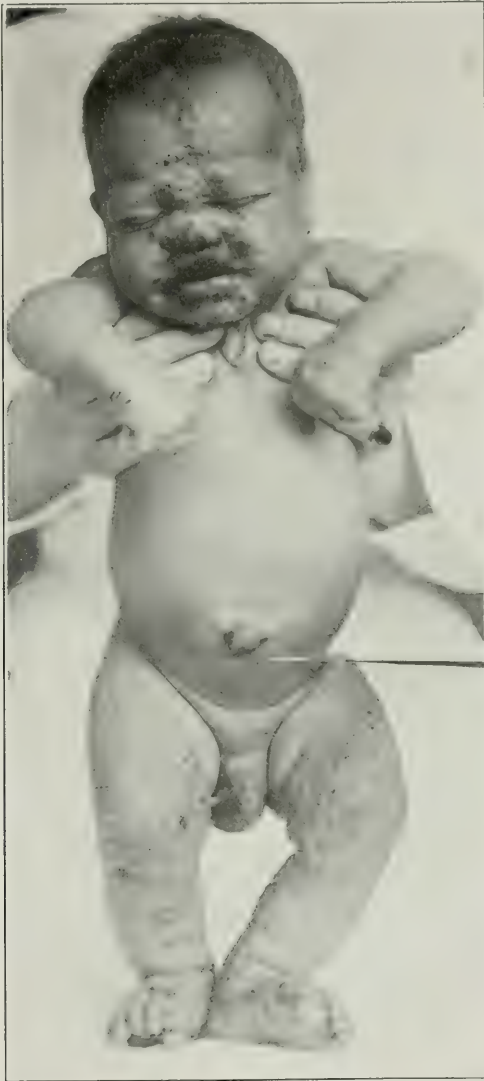


Fig. 1.—Eruption of hereditary syphilis before treatment. (Case 1.)

drying up, the moisture and hemorrhage ceasing in a manner almost magical. By the fifth day the face, except for a few fissures about the mouth, was almost clear and the eruption on the extremities much less marked. The only signs were a pigmentation of the skin of the extremities marking the site of the old crusts and the cicatrices about the mouth and lips (Fig. 2). The eosinophilia

diminished in one week to 11 per cent. and in three weeks to 3 per cent. In one week after the first injection the spirochetes could no longer be demonstrated. The improvement in general condition was not less striking than in the eruption.

The effect of salvarsan in lesions of the bones is well shown in the following case of multiple dactylitis:

CASE 2.—R. N., aged 2 months, admitted with multiple dactylitis; no coryza or eruption, but a typical history of syphilis. The extent of the osseous lesions



Fig. 2. The same patient five days after injection of salvarsan.

is shown in the x-ray pictures (Figs. 3 and 4) which portray marked changes in the first phalanges of the first and second fingers of the left, and of the second and third fingers of the right hand. In addition there was disclosed a similar lesion affecting the metacarpal bones of the second and fourth fingers of both hands. Externally the fingers showed only swelling, but no signs of acute

inflammation or breaking down. A dose of .05 gm. of salvarsan intravenously was given and repeated in two weeks. Within a week after the first dose there was an appreciable diminution in the size of the affected fingers and at the end of three weeks the hands were to all external appearances quite normal. The second radiograph was taken six weeks after the first and in it practically no traces of the previous lesion could be detected.

The effect of the treatment on the size of the liver and spleen was not so noticeable. Of nineteen patients who were followed long enough to make observations on this point possible, the size of the liver and spleen was unchanged in nine cases and markedly reduced in ten. Of seventeen patients in whom accurate observation of the lymph-nodes was possible, six showed definite reduction and no change was apparent in eleven cases. Improvement in the general condition of the patients as a rule corresponded to the change in the eruption, but was not quite so rapid nor so striking. In a few patients who were in very bad condition

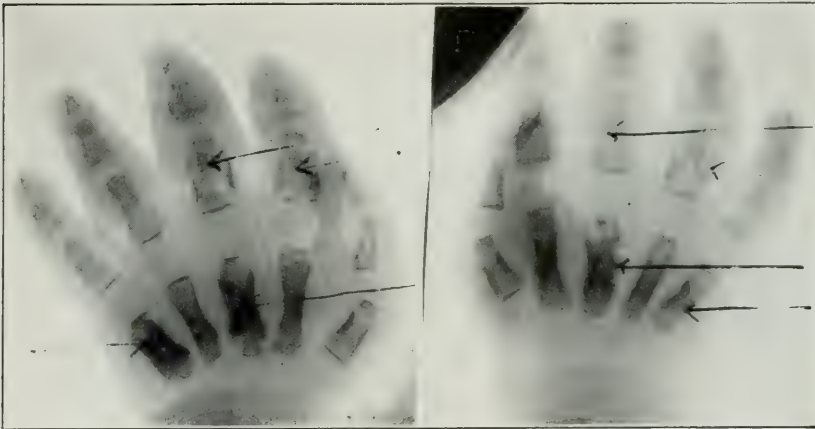


Fig. 3.—Syphilitic dactylitis before treatment. (Case 2.)

on admission, the injection of salvarsan was followed by marked retrogression in the cutaneous lesions without any corresponding improvement in the patients. Once begun, improvement in nearly all the patients continued unless the case was cut short by intercurrent disease. The following history is that of the only patient in whom a distinct relapse was seen in the syphilitic symptoms:

CASE 3.—T. M., aged 1 month, admitted with a severe infection, typical eruption and other symptoms of syphilis. Spirochetes were obtained from lesions about the buttocks and 0.1 gm. salvarsan was administered intravenously, followed by a second dose of the same size two weeks later. The symptoms and outward signs of syphilis rapidly disappeared after the injection and the child remained apparently well for two and one-half months when there was a recurrence of the eruption in typical form on the buttocks, and, as in the first instance,

the spirochetes were obtained from the lesions. A third dose, the same in size as in the two previous ones, was administered. This was followed as before by a rapid disappearance of the eruption and other symptoms. The child then remained apparently well for a period of three and one half months when the eruption again appeared in a fairly typical form and the spirochetes were obtained from the lesions. A fourth dose was now given and four and one-half months later a fifth dose. There has since been no return of the symptoms.

*Mortality and Causes of Death.*—If both the early and late deaths from hereditary syphilis are included, the mortality is very high. Considering that the cases here reported were taken in routine, and considering also the condition in which a number of the infants were at the time of admission, a death-rate of 50 per cent. during the period of about nine months for which these infants were followed is not high.



Fig. 4.—The same patient as in Figure 3, six weeks after salvarsan injection.

These results are certainly much better than we have seen in the hospital with the same class of patients with any other treatment. Eleven of the deaths were from intercurrent disease, seven being from acute bronchopneumonia and three from gastro-enteritis; we have included these among the fatal cases, although in four death occurred in from three to nine and one-half months after treatment was begun, and probably syphilis was only very remotely responsible for the fatal termination. The proportion of deaths due to syphilis itself is better shown in the early deaths. Thus three patients lived one week or less, and nine from one week to one month. The accompanying table (Table 1) gives the causes of death and the time after first injection of salvarsan.



There was only one case in which any untoward general symptoms could be ascribed to the salvarsan. In this patient the symptoms, progress and termination of the case strongly suggested a multiple neuritis, which was attributed to the arsenic. The dose was twice that given to other patients. The evidence in this case was not conclusive, but the history is highly suggestive. A general autopsy was not permitted, but a microscopic examination was made of a section of the median and musculospiral nerves by Dr. Wollstein, pathologist to the hospital. Nothing abnormal was found.

TABLE I.—CAUSES OF DEATH AND TIME AFTER FIRST INJECTION OF SALVARSAN

Case No.	Age	Cause of Death	Length of Time After First Injection
1	3 $\frac{1}{2}$ mo.	Bronchopneumonia . . . . .	4 days
2	5 mo.	Bronchopneumonia . . . . .	1 week
3	7 wks.	Bronchopneumonia . . . . .	3 weeks
4	3 wks.	Bronchopneumonia . . . . .	1 month
5	3 mo.	Bronchopneumonia . . . . .	1 month
6	1 mo.	Bronchopneumonia . . . . .	3 months
7	2 mo.	Bronchopneumonia . . . . .	9 $\frac{1}{2}$ months
8	2 $\frac{1}{2}$ mo.	Gastro-enteritis . . . . .	11 $\frac{1}{2}$ months
9	3 mo.	Gastro-enteritis . . . . .	6 months
10	13 mo.	Gastro-enteritis . . . . .	8 months
11	2 $\frac{1}{2}$ mo.	Acute peritonitis . . . . .	1 month
12	3 $\frac{1}{2}$ mo.	Syphilis . . . . .	15 hrs. after admission
13	6 wks.	Syphilis . . . . .	2 weeks
14	2 mo.	Syphilis . . . . .	3 weeks
15	5 mo.	Syphilis . . . . .	1 month
16	6 wks.	Syphilis . . . . .	1 month
17	5 wks.	Multiple neuritis . . . . .	1 month

CASE 4.—M. P., aged 5 weeks, admitted in wretched condition, suffering from a severe syphilitic infection. August 9, 0.1 gm. of salvarsan was given intravenously and the same dose repeated August 26; there was marked improvement in the local lesions and general condition during these three weeks. Two days after the second injection the cry seemed feeble, and two days later a slight icterus was observed; this rapidly increased during the next twenty-four hours and at the same time there was a weakness of the upper and lower extremities, which increased to complete paralysis, with absence of the knee-jerks. Examination of the blood showed white blood-cells, 55,000; red blood-cells, 1,170,000; polymorphonuclears, 85 per cent.; lymphocytes, 14.6 per cent.; eosinophils, 0.3 per cent.; hemoglobin, 48 per cent.; many normoblasts, megaloblasts, megalocytes and microcytes. Red cells showed in addition considerable vacuolation. Urin analysis revealed the presence of bile and occult blood. The general prostration and weakness steadily increased and five days after the paralysis was first noticed the child died apparently from respiratory involvement.

TABLE 2.—TABLE SHOWING RESULTS OF TREATMENT WITH

Case No.	Age.	Weight Lbs. Ozs.	Condition	Previous Treatment	Type of Infection	Spirochetes
1	1 mo.	9.5	Good	None	Severe	Present
2	10 mo.	17.0	Good	Mercury irregular for six months. (Inunct.)	Mild	Present
3	7 wks.	8.0	Fair	Mercury irregular since birth by mouth.	Mild	None found
4	3 mo.	11.5	Fair	None	Mild	Present
5	5 mo.	10.1	Poor	None	Mild	No external lesions
6	3½ mo.	7.2	Moribund	None	Severe	Present
7	1 mo.	7.11	Fair	None	Severe	Present
8	2 mo.	7.4	Fair	Mercury for one month irregular. (Inunction.)	Mild	No external lesions
9	3½ mo.	4.4	Bad	None	Severe	Present
10	2 mo.	5.8	Bad	None	Severe	Present
11	5 wks.	6.12	Fair	None	Severe	Present
12	2½ mo.	9.8	Fair	Mercury inunction off and on since birth.	Mild	Present
13	2 mo.	8.15	Fair	None	Severe	Present
14	13 mo.	8.15	Poor	None	Mild	No external lesions
15	5 mo.	10.8	Fair	Mercury inunction for 3 months.	Mild	No external lesions
16	2 mo.	7.7	Fair	None	Severe	Present

SALVARSAN OF INFANTS WITH CONGENITAL SYPHILIS

Date of Injection and Dosage	Wassermann	Result	Remarks
Nov. 21, '11—.05 gm. Jan. 11, '12—.05 gm.	Nov. 18, '11—Pos. Dec. 10, '11—Pos. Jan. 15, '12—Neg. Feb. 26, '12—Neg.	Died	Cause of death bronchopneumonia, Feb. 29, 1912. Free from all syphilitic manifestations and in good general condition before the final illness.
Dec. 7, '11—.05 gm. Apr. 3, '12—.05 gm. Jan. 9, '12—.10 gm.	Dec. 6, '11—Pos. Dec. 13, '11—Pos. Mar. 31, '12—Pos. June 29, '12—Pos. Oct. 10, '12—Neg.	Recovered	Examined in April, 1913. No syphilitic symptoms; in good condition.
Jan. 11, '12—.05 gm.	Jan. 9, '12—Pos.	Lost sight of	.....
Dec. 5, '12—.05 gm.	Dec. 3, '12—Pos. Dec. 13, '12—Pos.	Died	Cause of death bronchopneumonia, Dec. 28, 1912. Sick one week; syphilitic symptoms had disappeared.
Mar. 23, '12—.05 gm.	Mar. 20, '12—Pos.	Died	Cause of death bronchopneumonia, March 28, 1912. Sick one week. No improvement after injection.
Oct. 17, '12—.05 gm. Dec. 10, '12—.05 gm. Dec. 29, '12—.05 gm.	..... Dec. 9, '11—Pos. Jan. 15, '12—Pos. July 10, '12—Neg. Sept. 1, '12—Neg.	Died Recovered	Fifteen hours after admission. Examined in April, 1913. No syphilitic symptoms; in good condition.
Jan. 2, '12—.05 gm.	Dec. 25, '11—Pos. Mar. 30, '12—Neg. June 4, '12—Neg. Aug. 31, '12—Neg. Feb. 8, '13—Neg.	Recovered	Examined in April, 1913. No syphilitic symptoms; in good condition.
Apr. 13, '12—.05 gm.	Apr. 13, '12—Pos.	Died	Cause of death bronchopneumonia, fourth day after admission.
Apr. 13, '12—.05 gm.	Apr. 14, '12—Pos.	Died	In wretched condition on admission and died two days later of exhaustion.
Aug. 9, '12—.1 gm. Aug. 26, '12—.1 gm.	Aug. 9, '12—Pos. Aug. 31, '12—Pos.	Died	Cause of death multiple neuritis. Died twelve days after last dose. (Case reported in detail.)
Dec. 7, '11—.05 gm. Jan. 11, '12—.05 gm.	Dec. 10, '11—Pos.	Died	Cause of death acute gastro-enteritis, Feb. 1, 1912. Syphilitic symptoms had disappeared.
Dec. 16, '11—.05 gm. Jan. 2, '12—.05 gm. May 4, '12—.05 gm.	Dec. 15, '11—Pos. Mar. 30, '12—Neg. May 5, '12—Neg. May 15, '12—Neg. Aug. 4, '12—Neg.	Died	Cause of death bronchopneumonia, Aug. 12, 1912. Sick two weeks; syphilitic symptoms had disappeared.
Apr. 29, '12—.05 gm. May, 8, '12—.05 gm. June 28, '12—.1 gm. Nov. 2, '12—.1 gm.	Apr. 28, '12—Pos. May 2, '12—Pos. June 27, '12—Pos. Aug. 11, '12—Pos. Sept. 8, '12—Pos. Oct. 10, '12—Pos.	Died	Cause of death, acute enterocolitis, Nov. 27, 1912. Sick one week: free from syphilitic symptoms and in good general condition.
Dec. 9, '11—.05 gm. Dec. 30, '11—.05 gm.	Dec. 8, '11—Neg.	Died	Cause of death, syphilis, Feb. 6, 1912. No improvement after injections.
May 24, '12—.05 gm. June 18, '12—.05 gm. Oct. 16, '12—.1 gm. Dec. 12, '12—.1 gm.	May 24, '12—Pos. Aug. 4, '12—Neg. Oct. 10, '12—Pos. Jan. 1, '12—Neg.	Recovered	Examined in April, 1913. No syphilitic symptoms; in good condition.

TABLE 2.—TABLE SHOWING RESULTS OF TREATMENT WITH

Case No.	Age.	Weight Lbs. Ozs.	Condition	Previous Treatment	Type of Infection	Spiro- chetes
17	2½ yr.	28-12	Fair	Mercury inunction irregular from birth.	Mild	No external lesions
18	3 mo.	8-12	Fair	None	Mild	Present
19	7 mo.	12-5	Fair	Mercury internally for one week.	Mild	No external lesions
20	21 mo.	21-15	Fair	Mercury and iodid irregular from birth.	Mild	No external lesions
21	4 mo.	11-4	Fair	None	Severe	Present
22	4 mo.	10-3	None	None	Mild	No external lesions
23	1 mo.	8-5	Fair	None	Severe	Present
24	6 wks.	9-5	Fair	None	Mild	No external lesions
25	3 wks.	7-0	Poor	None	Severe	Present
26	4½ yr.	32-0	Fair	Mercury by mouth irregular from birth.	Mild	No external lesions
27	1½ yr.	17-0	Fair	Mercury by mouth irregular from birth.	Mild	No external lesions
28	6 wks.	8-0	Bad	None	Severe	Present
29	7 wks.	7-0	Bad	None	Severe	No external lesions
30	4 mo.	7-8	Poor	None	Severe	Present
31	6 wks.	10-11	Fair	None	Severe	Present
32	6 wks.	5-8	Poor	Mercury inunction for two weeks.	Severe	Present
33	4 mo.	8-0	Fair	None	Mild	Present
34	2½ mo.	6-13	Poor	None	Severe	Present



SALVARSAN OF INFANTS WITH CONGENITAL SYPHILIS—*Continued*

Date of Injection and Dosage	Wassermann	Result	Remarks
May 11, '12—.1 gm. June 6, '12—.1 gm.	May 8, '12—Pos. June 4, '12—Pos. July 18, '12—Neg. Sept. 20, '12—Pos. Sept. 27, '12—Pos.	Recovered	Examined in April, 1913. Great improvement in general condition and free from syphilitic symptoms.
May 11, '12—.1 gm.	May 22, '12—Pos. July 1, '12—Neg. Oct. 10, '12—Neg.	Died	Cause of death acute gastro-enteritis, Oct. 12, 1912. Free from syphilitic symptoms.
May 15, '12—.05 gm. June 6, '12—.1 gm. July 6, '12—.1 gm. Dec. 12, '12—.1 gm.	May 15, '12—Pos. June 4, '12—Pos. July 1, '12—Pos. Aug. 4, '12—Pos. Oct. 10, '12—Pos. Dec. 13, '12—Neg. Feb. 23, '12—Neg.	Recovered	Examined in April, 1913. Great improvement in general condition and free from syphilitic symptoms.
May 5, '12—.1 gm. June 6, '12—.1 gm. July 15, '12—.2 gm. Dec. 12, '12—.2 gm.	May 15, '12—Pos. June 4, '12—Pos. July 1, '12—Pos. Aug. 31, '12—Pos. Oct. 10, '12—Pos. Dec. 13, '12—Pos. Feb. 23, '13—Neg.	Recovered	Examined in April, 1913. In good condition and free from syphilitic symptoms.
May 14, '12—.05 gm. June 6, '12—.1 gm. July 6, '12—.1 gm.	May 15, '12—Pos. July 1, '12—Pos. Aug. 4, '12—Neg. Oct. 17, '12—Neg. Feb. 23, '13—Neg.	Recovered	Examined in April, 1913. In good condition and free from syphilitic symptoms.
Aug. 11, '12—.1 gm. Aug. 26, '12—.1 gm. Oct. 17, '12—.1 gm.	Aug. 12, '12—Pos. Aug. 31, '12—Pos. Oct. 10, '12—Pos. Jan. 23, '13—Neg.	Recovered	Examined in April, 1913. In good condition and free from syphilitic symptoms.
July 15, '12—.1 gm. Aug. 13, '12—.1 gm. Oct. 3, '12—.1 gm. Jan. 22, '13—.1 gm.	July 20, '12—Pos. Aug. 3, '12—Pos. Jan. 23, '13—Pos.	Recovered	Examined in April, 1913. Great improvement; no syphilitic symptoms. (Case reported in detail.) Two relapses.
Apr. 29, '12—.05 gm. May 24, '12—.05 gm. July 6, '12—.05 gm.	May 1, '12—Pos. July 1, '12—Neg. Oct. 10, '12—Neg. Feb. 23, '13—Neg.	Recovered	Examined in April, 1913. Great improvement in general condition and free from syphilitic symptoms.
Sept. 23, '12—.05 gm. Oct. 13, '12—.05 gm.	Sept. 21, '12—Pos. Oct. 11, '12—Neg.	Died	Cause of death, bronchopneumonia. General condition fair; free from syphilitic symptoms.
July 23, '12—.2 gm. Sept. 9, '12—.2 gm.	June 1, '12—Pos. Sept. 8, '12—Pos.	Recovered	Examined in April, 1913. In good general condition and free from syphilitic symptoms.
July 23, '12—.1 gm. Sept. 9, '12—.2 gm.	June 1, '12—Pos. Sept. 8, '12—Pos.	Recovered	Examined in April, 1913. In good general condition and free from syphilitic symptoms.
Aug. 19, '12—.1 gm.	Not done	Died	Cause of death syphilis, Aug. 26, 1912. Some improvement had occurred in cutaneous lesions.
Nov. 18, '12—.05 gm.	Nov. 8, '12—Pos.	Died	Cause of death, bronchopneumonia, Nov. 25, 1912. No improvement.
Dec. 11, '12—.05 gm. Jan. 4, '13—.05 gm.	Dec. 9, '12—Pos. Jan. 12, '13—Neg.	Recovered	Examined in April, 1913. In good general condition and free from syphilitic symptoms.
Jan. 8, '13—.05 gm. Jan. 22, '13—.05 gm.	Jan. 25, '13—Pos.	Recovered	Examined in April, 1913. In good general condition and free from syphilitic symptoms.
Nov. 25, '12—.05 gm. Dec. 11, '12—.05 gm.	Not done	Died	Cause of death bronchopneumonia, Jan. 1, 1913. Doing well till onset of pneumonia and free from syphilitic symptoms.
Oct. 26, '12—.05 gm. Nov. 9, '12—.05 gm.	Oct. 26, '12—Pos. Feb. 23, '13—Pos.	Recovered	Examined in April, 1913. In good general condition and free from syphilitic symptoms.
Jan. 15, '13—.05 gm. Feb. 3, '13—.05 gm.	Jan. 23, '13—Pos. Feb. 8, '13—Neg.	Died	Cause of death acute streptococcal peritonitis. Marked improvement had occurred in syphilitic symptoms.

## CONCLUSIONS

1. Immediate and striking benefit follows the injection of salvarsan in hereditary syphilis, and this is seen in many patients in whom mercury has been used with little or no apparent benefit.

2. Salvarsan must be given intravenously; with the technic which we have described its administration is not difficult and it is practically free from danger.

3. A single dose of salvarsan does not cure hereditary syphilis, although it often removes the visible symptoms. Relapses, however, are to be expected unless the dose is repeated. With present experience it seems advisable to repeat the injections at intervals for one year, even though no symptoms are present.

4. The best results in hereditary syphilis are undoubtedly obtained by the early use of salvarsan followed by mercurial treatment.

5. Even with the aid of the Wassermann reaction it is difficult to say when a child with hereditary syphilis is actually cured.

## RESULTS OF TREATMENT WITH SALVARSAN IN LATE CONGENITAL SYPHILIS \*

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During the past year we have treated with salvarsan eighteen children who were suffering from congenital syphilis. Our results as regards the Wassermann reaction were so surprising to ourselves that we searched the literature to ascertain the results of others and found so few reports controlled by the laboratory test that we think it worth while to report our cases.

Although the literature on salvarsan treatment is now enormous, very little work has been reported on its use in congenital syphilis. Among British writers, McDonagh<sup>1</sup> reports a case, aged 15 years, with disappearance of clinical signs, but with the Wassermann reaction positive after one dose. Sequeira<sup>2</sup> reports one case, also aged 15 years, in which he gave four doses of salvarsan intramuscularly; the remainder of his congenital cases were infants. In his cases the symptoms disappeared, but the reaction remained positive. He seldom gave more than one dose. Marshall<sup>3</sup> denounces salvarsan. Eddington and Browning<sup>4</sup> had a patient aged 16 years with a syphilitic knee. After two doses (0.2 and 0.27 gm.) of salvarsan the reaction became negative. Bunch<sup>5</sup> obtained a negative reaction in an infant of 8 weeks after two administrations, but an infant of 14 weeks was still positive after two doses.

In American literature the reports are merely reports of a few cases, and the effect of the Wassermann reaction is seldom mentioned. De Buys<sup>6</sup> reports three cases. He advises treatment through the mother's milk, and says salvarsan should only be used as an adjunct to mercury and potassium iodid.

The most thorough reports are by German and Austrian writers, but their reports are mostly on the treatment of nurslings through the

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\* Submitted for publication May, 1913.

1. McDonagh, J. E. R.: *Brit. Jour. Child. Dis.*, October, 1910.

2. Sequeira: *Brit. Jour. Child. Dis.*, February, 1911.

3. Marshall: *Brit. Jour. Child. Dis.*, March, 1911.

4. Eddington and Browning: *Glasgow Med. Jour.*, October, 1911.

5. Bunch: *Brit. Jour. Child. Dis.*, April, 1912.

6. DeBuys: *AMER. JOUR. DIS. CHILD.*, January, 1913.

7. Herxheimer and Reinke: *Deutsch. med. Wehnschr.*, September, 1910.

mother's milk. Herxheimer and Reinke<sup>7</sup> report two fatal cases, both infants aged 2 months, and both dying four days after the administration. At autopsy arsenic was found in all the organs, but no treponema, except in the lungs, where they were agglutinated and markedly degenerated. Welde<sup>8</sup> treated twenty-eight patients, partly by subcutaneous and intramuscular injection, but his later cases by the intravenous method. His average dose was 0.1 gm., but most of his cases were in infants and received only one administration. The symptoms disappeared, but in only one case did the Wassermann become negative, and then it became positive again. No bad effects were observed.

We have treated eighteen patients; only three of these were under 5 years of age; most of them were suffering from bone lesions or interstitial keratitis. At the outset of our work, like most workers at that time, we believed that one or two doses would cure nearly all cases of syphilis, but by testing the Wassermann reaction after each administration we found it positive, and as the clinical symptoms did not entirely disappear in several cases we repeated the administration. Our method of procedure at first was to give salvarsan about once a month and test the reaction a month later. Later we gave a dose every week or every second week and tested the reaction usually between forty-eight and seventy-two hours following. We did not consider the reaction as finally negative unless the blood was tested between forty-eight and seventy-two hours after an administration, and we agree with McDonagh as to the value of a provocative dose, both in congenital and acquired syphilis. In ninety-nine administrations we used the intravenous method, except in one case (E. M.), who being mentally deficient, resisted, and we had to resort to intramuscular administration. To one who is experienced in giving intravenous injections the small veins of children do not offer a great obstacle. In most cases we used the median basilic or median cephalic veins, but occasionally we had to use the external jugular, placing the child in position advised by Wollstein and Morgan<sup>9</sup> for blood-culture work. In only one case, a marantic infant of 6 months, did we fail to enter a vein.

The amount given varied according to the weight of the child. Taking 150 pounds as the average male adult weight and 0.6 gm. salvarsan and 0.9 gm. neosalvarsan as average doses for that weight, we dissolved the salvarsan in 300 c.c. of distilled water and the neosalvarsan in 150 c.c. Of the latter we gave 1 c.c. and of the former 2 c.c. for each pound of weight of the patient.

8. Welde: München. med. Wehnschr., April, 1912.

9. Wollstein and Morgan: AMER. JOUR. DIS. CHILD., October, 1912.



## THE CLINICAL RESULTS

The administration of salvarsan was in all cases followed by improvement in the physical signs. In no case did the symptoms resist repeated doses, although in one case (C. B.) there was a recurrence of symptoms one month after treatment had been discontinued, the patient having received nine doses. Three patients were babies suffering from wasting and rashes. All three were cured as regards symptoms. Seven patients suffered from interstitial keratitis. The inflammation of the cornea subsided in all cases, leaving, of course, scars, but the subsidence was at least as rapid as with mercury. C. B., aged 10 years, improved rapidly after the fourth dose and also showed marked improvement in his general health, but his symptoms recurred as mentioned above, and he again failed in general condition. Under mercury he improved again. He is the only patient in whom the treatment did not prove satisfactory. He also showed syphilitic arthritis of both knees, which was entirely cured, leaving no deformity. Seven of the patients were cases of bone syphilis, three affecting the nasal bones and causing severe ozena. The symptoms in all except the nasal cases subsided rapidly; one (R. D.) relapsed two months after her first dose, but her symptoms have entirely disappeared after four more doses. The nasal cases have all improved, but are slower and are still under treatment.

One patient had no symptoms except poor bodily development and Hutchinson's teeth. His Wassermann reaction was doubtful, that of his mother positive. He was only given one dose, after which his reaction was negative.

With the exception of R. D., all the children were under-sized and poorly nourished. The improvement in their general health was marked, resembling the improvement after operations in severe cases of enlarged tonsils and adenoids.

The only untoward results noticed were that three bone cases developed mild interstitial keratitis after treatment was begun, and one patient developed it in his right eye while undergoing treatment for the left. In no case were there severe symptoms following the administration, and after the neosalvarsan seldom any nausea at all. Some of them had vomiting for twelve to twenty hours after the administration of the original salvarsan.

## THE EFFECTS ON THE WASSERMANN REACTION

As will be seen in the table, only five cases gave a negative reaction following treatment.

A. S., aged 6 months, was positive before treatment, received one dose of neosalvarsan and then for four months mercury by inunction. She then reacted negatively.

A. W., aged 17 months, reacted negatively after three doses, but his blood was not tested previously. His mother's blood was positive.

H. P., aged 12, reacted negatively after his eighth dose of neosalvarsan.  
 T. C., aged 12, received three doses of salvarsan and then three doses of neosalvarsan, after which he reacted negatively.  
 H. F., referred to above, reacted doubtfully before and negatively after one dose of neosalvarsan.

TABLE SHOWING EFFECT OF TREATMENT ON WASSERMAN REACTION

No.	Case	Age Yrs.	W. R. Before Treatment	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.	Dose No.	W. R.	Dose No.
1	A. S.	5/12	++	1	—	2	—	3	—	3	—	3	—	3	—	3	—	3	—	3
2	A. W.	15/12	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
3	M. C.	15/12	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
4	M. D.	5	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
5	A. M.	6	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
6	R. F.	7	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
7	H. P.	7	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
8	C. C.	9	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
9	W. P.	10	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
10	C. B.	10	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
11	T. C.	11	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
12	H. F.	11	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
13	P. S.	12	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
14	E. M.	13	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
15	R. D.	15	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
16	W. W.	24	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
17	F. E.	9	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2
18	N. H.	7	++	1	++	2	++	2	++	2	++	2	++	2	++	2	++	2	++	2

The results of treatment on the Wassermann reaction can hardly be considered satisfactory, except as they compare favorably with the results obtained by mercurial treatment.

Gummata, periostitis and ulcers disappeared rapidly. Keratitis, which was present in eight cases, healed, we believe, more rapidly than under mixed treatment, and the resulting scars were therefore less. The results

were better than those obtained with mercury, and in about half of the cases followed treatment by mercury where the latter had been of little benefit.

Latterly we have used larger doses, and in future we shall use more intensive treatment, as large doses as the patient can stand and at shorter than seven-day intervals.

Nearly all the patients were treated in the out-patient department of the hospital and were sent home in a few minutes.

#### CONCLUSIONS

1. All our own cases improved clinically under salvarsan treatment.
2. The intensity of the Wassermann reaction diminished steadily with frequently repeated full doses, but in nine patients over 4 years, who received four doses or more, only two became negative, and that after eight and nine doses.
3. The younger the child, the more quickly does the Wassermann reaction become negative.
4. We have not found the administration of salvarsan by intravenous injection in children to produce any bad effects.

## A RAPID CLINICAL METHOD FOR THE ESTIMATION OF TOTAL FAT IN INFANTS' STOOLS \*

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One of the great disadvantages in the study of the digestive disturbances of infancy is our inability to determine quickly the quantity of fat present in an infant's stool. Qualitative tests, while of value, do not suffice, for under normal conditions we may encounter neutral fat, free fatty acids and soaps in an infant's stool. Our requirements will not be fulfilled until we have some approximate method for determining the neutral fats, free fatty acids and the soaps as they exist in the stool when it leaves the body, or, in other words, as they exist in the intestine uninfluenced by external agencies.

In pursuance of this need we began last September to study the various methods now in use for the estimation of fat in stools with the hope that we might find a way of shortening some of the existing methods, or of combining the different principles involved into a new or modified method. The methods we have investigated more in detail are the Kumagawa and Suto, Friedrich Müller, Keller's modification of Röhmann's and the Folin-Wentworth method. Hoffman's copper acetate method, a qualitative method with approximate relative quantitative possibilities, did not give us satisfactory results.

From our investigation we believe the Folin-Wentworth method comes the nearest being accurate of any of the methods considered. We base our opinions not on long or continued use of any of these methods, but on the principles involved. The Folin-Wentworth method, however, does not give us what we want. It determines only the neutral fat, the fatty acids, including the fatty acid of the soaps, and the total fats. If we regard the free fatty acids in the stool of little importance, as some have done, we may then regard the figures obtained for fatty acids as representing the soaps. We believe, however, that we are not justified in disregarding the free fatty acids, for under some conditions they are not insignificant. The Folin-Wentworth method is not a clinical method. It requires from twenty-one to twenty-four hours to complete it, providing the extracting apparatus can be kept running the full twenty-hour period. It is suitable for careful metabolism work, but even here there

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\* From the Pediatric and Pharmacy Departments, University of Michigan.

\* Read at the meeting of the American Pediatric Society, Washington, D. C., May, 1913.



are times, as we shall show later, when it fails to extract all the fat from a sample of stool.

One of us had been endeavoring for some time to develop a centrifugal method for the estimation of total fat. Being unable to get uniform results, we abandoned this method and directed our attention to an investigation of the rate of extraction with acid-ether according to the Folin-Wentworth method. Our results will be found in Table 1.

TABLE 1.—RESULTS OF EXTRACTION OF FAT FROM STOOLS BY THE ACID-ETHER METHOD

Sample 3. Pulverized Stool After Extracting.	Neutral Fat, Per Cent.	Fatty Acids, Per Cent.	Total Fat, Per Cent.	Total Fatty Substance, Per Cent.
Fractional Experiment*—				
One hour .....	1.73	17.69	19.42	37.20
Five hours more.....	0.02	22.36	22.38	42.87
Fourteen hours more.....	0.50	9.90	10.40	19.92
Total .....	2.25	49.95	52.20	99.99
Sample 3 extracted the full twenty hours .....	4.49	45.49	49.98	.....
Difference in total result...	+ 2.24	— 4.46	— 2.22	.....

\* In this experiment a new weighed flask was substituted at the end of each run. The extraction was kept running the full twenty-hour period.

From this experiment it will be seen that the bulk of the neutral fat appears to be extracted at the end of the first hour, and the bulk of the fatty acids (produced by the action of the acid ether on the soaps) is extracted at the end of the sixth hour.<sup>1</sup> In other words, 76.88 per cent. of the neutral fat comes out in one hour, 82 per cent. of the fatty acids in six hours, and 80 per cent. of the total fat in six hours. It will be further observed that in the sample undergoing undisturbed extraction for twenty hours, over twice as much neutral fat is obtained and the amount of total fat is over 2 grams less than that obtained in the frac-

1. The formation of fatty acids from soaps is what is termed a substitution process. It is readily effected with weak acids. The following experiment shows how completely the acid ether extracts a sample of soap. We took of

Pure castile soap, gm.....	1.1035
Extracted 12.5 hours with N/10 acid ether. Weight of substance after extraction, gm.....	1.1142
Weight of substance unextracted by petroleum ether, gm.....	0.0412

Fatty acids recovered from the soap. By subtraction, gm.....	1.0623
By titration, gm. ....	1.0516

tional experiment. From this we conclude that the cold acid-ether process of extraction cannot be utilized for clinical purposes in the sense of giving us data on the three varieties of fat encountered in an infant's stool. We thought some importance might attach itself to the fact that the bulk of the neutral fat came out during the first hour's extraction, but the difference between the neutral fat figures for the fractional extraction experiment and the undisturbed twenty-hour extraction experiment is so great we feel that this process cannot be depended on for quick estimation of the neutral fat in a stool.

We next set ourselves the task of endeavoring to shorten the drying period. We encountered stools which dry more readily than others, and stools, which, in spite of many hours drying in the closed hot-air oven and subsequently many months (nine) desiccation over  $\text{H}_2\text{SO}_4$ , fail to remain in powdered form after passing through a forty-mesh sieve. We constructed a drying oven<sup>2</sup> through which a constant current of hot air passed, the stool sample being placed on a shelf over and under which the air circulated. By this method we were able to reduce the drying time one-half. Drying the stool with alcohol also shortens the period, and in many instances, but not in all, this method proved to be the shorter one. By this means the water is taken out with the boiling alcohol and the alcohol finally carefully evaporated off.

After the trial of other methods of extraction, hot alcohol, etc., and titration methods without, as yet, satisfactory results, we again turned our attention to our centrifugal method which determines the total fat only. At times we had succeeded in removing comparatively large amounts of fat from infants' stools by this method, while at other times with samples of the very same stool, and apparently exactly the same manipulations, we got only blank or negative results. The principle of the centrifugal method is the conversion of all fat and soaps into fatty acids, which are later brought into the graduated stem of a centrifugal tube and the amount in cubic centimeters read off directly.

In our effort to obtain uniform results three difficulties presented themselves:

1. A whitish substance almost invariably appeared floating on the surface of the centrifugalized fluid, and later it appeared below or

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2. The oven is easily constructed. One length of Russia iron pipe  $3\frac{1}{2}$  to 4 inches in diameter is connected at each end with a circular elbow. At one end the elbow is turned down over a Bunsen burner, at the other the elbow is turned up and a thermometer suspended in it by means of a wire. An opening about 5 inches long is cut into the side of the pipe length and the flap turned into the pipe to form the shelf. A lid or door is hinged above the opening and is kept closed by means of a simple turn catch attached to the lower edge of the lid. The catch fits into a hole punched in the outer edge of the shelf flap. A brisk current of hot air passes through the pipe and the temperature is easily regulated with the ordinary Bunsen.

intimately mixed with the fat column in the stem of the tube after final centrifugalization. In some samples of stool in which no fat was present this substance rose to the top and sometimes resembled quite closely a poor fat layer.

2. Carbonization of the fat layer frequently took place because of an excess of acid. After a number of trials on different stools we were able to determine the maximum and minimum amount of acid necessary to burn the organic matter other than the fat and set the fat free, and to work out an optimum concentration which seems to be adaptable to most stools.

3. At times the fat column was difficult to read.

After milk fat passes through the intestinal canal certain physical changes take place. Before ingestion a centrifugal test shows a clear, fluid, yellow fat layer, which becomes more firm as it cools. It remains, however, in this clear condition for several minutes and is easily read. After the milk passes through the digestive tube a centrifugal test shows a denser and darker fat layer, which solidifies at a higher temperature and contracts in such a way as frequently to cause it to break in the center. A reading made when first taken from the machine is frequently a little greater than it is a minute or two later. If the tube is immersed in hot water the fat column melts and again occupies its former position in the tube. There is evidently a change in the specific gravity of the fat after it has passed through the intestinal tube. This difficulty seemed to be almost as insurmountable as the first one, which we will return to later. We thought to alter the specific gravity (lower the melting point) of the fat present in the stool by adding a known quantity of a fatty acid of low melting point. By deducting the difference in the result obtained we hoped to find the total fat content. We chose *oleic acid*. We were able to recover from stools and substances free from fat the amount of oleic acid added, and in stools with a fat content we were able to recover the oleic acid plus additional fat from the stool.<sup>3</sup> The fat column was by this means made clear. Such a method we believe is not acceptable from a chemical or clinical standpoint, for we are introducing a factor. The introduction into a stool of a substance sought might easily lead to error. We found, as we have stated, that much of our trouble with the fat column came from carbonization induced by adding too concentrated acid.

At this point in our investigation we came across Kita's<sup>4</sup> work on a similar method for the estimation of fat in meat. He had encountered the same difficulty with the appearance of a white substance on the top of the centrifugalized fluid, and found by adding a small amount of amyl alcohol complete separation of the fat layer was effected. We found

3. See foot note to Table 2.

4. Kita, T.: Arch. f. Hyg., 1904, li, 165.



this to be the case when we added amyl alcohol to our stool mixture. As is quite generally known, the addition of a small amount of 80 per cent. ethyl alcohol straightens out the fat column in the determination of fat in cheese by the Babcock method so that it can be easily read. Our experience with ethyl alcohol, however, has not been satisfactory. Because of its low boiling point (78 C.) when it is added to the hot acid stool mixture, some of the contents are often blown out through the stem of the tube. Kita gives no explanation for the use of amyl alcohol. The alcohol in either case effects a better separation of the fat, and we believe the advantage gained from the use of amyl alcohol lies in its very high boiling point (131 C.). By means of the addition of amyl alcohol, our fat layer now became as clear as we could wish it to be. By immersing the tube in hot water after centrifugalization the amount recovered is easily read off. As a precautionary measure we found it necessary that the amyl alcohol should be thoroughly mixed with the acid water stool mixture, otherwise it would come up into the stem of the tube, and, because of its acquired yellow color, appear as a fat column. We have worked out the following method, which has given us very uniform and apparently quite accurate results:

CENTRIFUGAL METHOD FOR ESTIMATION OF TOTAL FAT IN  
INFANT'S STOOLS

*The Sample.*—If pulverized stool is examined, one-quarter (0.25) gram should be carefully weighed. If fresh or moist stool is examined, one-half (0.5) gram. An inexpensive prescription balance is sufficiently accurate for clinical purposes. For more careful work an analytical balance is of course necessary. The stool, if dry, is best weighed in a poised watch glass and transferred to glazed paper. Moist stool is quite easily removed by means of a spatula from glazed paper on which it is weighed, or from the watch glass, by means of water. The sample is carefully rubbed up in a thin-lipped mortar. A maximum of 20 c.c. of warm (40 to 50 C.) distilled water is used to transfer the mixture to a Babcock milk bottle graduated in *fiftieths*. A little practice enables one to transfer the entire sample with the first 10 c.c. of water, leaving the remainder to rinse off the mortar and pestle.

1. To the sample, now thoroughly mixed, 17.5 c.c.  $H_2SO_4$  (1.84) is added. Great care should now be taken to mix thoroughly by shaking the bottle back and forth vigorously (it should be remembered that all the organic material except the fat must be completely burned, or the test will be a failure).

2. One c.c. amyl alcohol is now added and thoroughly mixed.

3. The tube is now carefully counterpoised and centrifugalized for three minutes at high speed. Enough hot water is then added to bring



the fat into the graduated portion of the stem of the bottle. The bottle is again counterpoised, centrifugalized for one minute and the number of divisions on the stem occupied by the fat read off. Care must be taken to keep the stem hot and all readings must be made while it is hot. This is quickly accomplished by immersing the bottle in a pitcher or beaker of hot water.

*Calculation.*—If 0.25 gram of stool has been used, multiply the number of divisions on the stem of the tube occupied by the fat column by the factor 7.2; if 0.5 gram sample of stool is used, multiply by the factor 3.6; the result is the percentage of fat in the sample examined.

TABLE 2.—COMPARISON OF CENTRIFUGAL METHOD WITH FOLIN-WENTWORTH METHOD

Stool No.	Food Given.	Character of Sample	Percentage of Fat Obtained by the						
			Centrifugal Method. Analysis No.				Folin Wentworth Method. Analysis No.		
			1	2	3	4	1	2	3
1	Eiweissmilch..	Pulverized.	36.00	36.00	36.00	.....	36.32	.....	.....
3	Eiweissmilch..	Pulverized.	43.08	43.23	.....	.....	49.98	52.20	.....
8	Eiweissmilch..	Pulverized.	36.00	32.40	32.40	32.40	34.52	35.24	.....
9	Breast milk...	Moist* ....	16.20	16.20	16.20	16.20	.....	.....	.....
11	Breast milk...	Pulverized.	50.40	50.40	50.40	.....	34.70	35.30	34.60
							Centrifugal test on sedi- ment left in extraction capsule.....		14.40
									49.00

\* Oleic acid method. By substituting 0.1 c.c. oleic acid for the amyl alcohol and rubbing it well into the stool we obtained with a sample of this stool 34.20 per cent. fat. Subtracting the oleic acid value, 18 per cent., we obtained exactly the same result, 16.20 total fat.

To determine the amount of fat in the twenty-four-hour sample of stool, the stools may either be weighed when passed, or they may be kept in a moist chamber and weighed at the end of the period. The former is the better method, for, by this means any loss or gain in weight may then be detected and accounted for. The stool from which the sample is taken must be thoroughly mixed. From the known weight of the stool the total amount of fat is readily estimated. With a little practice a complete test can be made in ten minutes.

*Sensitiveness of the Centrifugal Test.*—Table 2 records a few comparative tests with the Folin-Wentworth method.

It will be observed that in most instances the centrifugal method gives practically the same reading on the same stool. It is not subject to as many variations as the extraction method. It will be further observed that for some unexplained reason at one time it gave a lower percentage than the extraction method. In another rather striking instance the centrifugal method gave a much higher reading than the extraction method. In the last instance we were able to demonstrate that the acid ether failed to extract 14 per cent. of the fat after twenty-six hours' extraction in the Soxhlet apparatus, and that the addition of this amount to that previously obtained by the extraction method was almost the same as the figures obtained by our centrifugal method. Furthermore, in the case of the third analysis (No. 11), Folin-Wentworth, only 0.5 gram sample of stool was used and run for twenty-six hours, which is the equivalent of fifty-two hours on 1 gram, and yet we were able to extract no more fat than in the other two cases.

We believe the true fat content of this sample of stool would not have been known had we depended on the Folin-Wentworth method. This is the breast-milk stool previously referred to, which resisted pulverization, even after nine months' drying over  $H_2SO_4$ . After rubbing this sample through a fine sieve, it persisted in forming little balls and coffee-ground-like masses. These doubtless resisted extraction by the cold acid ether. The hot acid water mixture of course readily overcomes this difficulty. In the one case extraction is at work; in the other, liberation.

We believe a knowledge of the total fat content of stools may prove to be of value in the diagnosis and treatment of the digestive disturbances of infancy, and we hope this simple method, based on the Babcock principle, will help to further our knowledge in this field of medical research.

# PROGRESS IN PEDIATRICS

## RÉSUMÉ OF THE RECENT LITERATURE ON MENINGITIS (NOT INCLUDING MENINGOCOCCUS MENINGITIS)

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### INCIDENCE

In 197 cases, Holt found the incidence of the various forms of meningitis as follows:

Tuberculous meningitis .....	138
Pneumococcus meningitis .....	22
Meningococcus meningitis (sporadic).....	24
Staphylococcus and streptococcus meningitis.....	10
Influenzal meningitis .....	4
<i>Bacillus coli</i> meningitis.....	1
	<hr/>
	199
Counted twice, mixed infections.....	2
	<hr/>
	197

Tuberculous meningitis is, according to Holt,<sup>1</sup> twice as prevalent during March, April and May as in any other similar period. The number of cases increase in the spring, being highest during April. In summer and early fall, the lowest number of cases are seen. The most plausible explanation for the seasonal prevalence of tuberculous meningitis is that in these cases there had been a previous infection of the respiratory tract, usually of the bronchial nodes, which was latent. As a result of an acute respiratory infection, which occurs so commonly in the winter and spring months, the tuberculous process becomes active and spreads rapidly. This is apparently supported by the fact that at autopsy pulmonary lesions are invariably present, although in the great majority of the cases no pulmonary signs are demonstrable during life. The greatest number of cases are seen between the ages of 9 and 12 months. This may be due to closer exposure to infected adults at this period of life. In nearly all cases, exposure to pulmonary tuberculosis of the adult could be traced. This was also shown by a study of the type of the tubercle bacillus found in the cases of tuberculous meningitis. In 32 cases human bacilli were found in 30, bovine bacilli in 1, and both

1. Holt: AM. JOUR. DIS. CHILD., 1911, i, 26.

types in 1. From the number of cases of pneumococcus meningitis reported in the literature one might gain the impression that this form of meningitis is a frequent complication of pneumonia. Its infrequency, however, is well shown by the statistics of Rolly.<sup>2</sup> During 1904-1909, amongst 1,050 cases of pneumonia at the University Klinik at Leipzig, only 6 cases of pneumococcus meningitis were observed.

During the period of non-epidemic occurrence of meningococcus meningitis, 70 per cent. of all of cases of meningitis in infancy are, according to Morse, of the tuberculous variety.

The frequency of influenzal meningitis is shown by the fact that at the beginning of the year 1911, Martha Wollstein<sup>3</sup> was able to report on 49 cases of pure infections, and 9 cases of mixed infections. Of these, 28 were under 1 year of age; only 5 were in adults. Pisek, in 1912, speaks of 58 cases, only 5 of which were in adults.

#### PATHOLOGY

Oseki<sup>4</sup> has shown that when meningeal symptoms occur in the course of acute infectious diseases, the macroscopic examination of the nervous system alone is not sufficient to exclude the existence of organic changes. A careful microscopic examination often reveals the presence of a leukocytic infiltration of the meninges of the brain and cord. Not infrequently the same changes are demonstrable even when no meningeal symptoms have been observed during life. In a number of cases, inflammatory lesions were present in the parenchyma of the brain, but not in the meninges. In thirteen out of sixteen cases, Oseki found in the meninges or central nervous system, bacteria which were identical with those of the original disease.

Kirchheim and Schroeder<sup>5</sup> call attention to the fact that in acute infectious diseases, pathologic changes may be demonstrated in the central nervous system without there having been symptoms during life referable to the nervous system. It is, however, more common to find no changes where symptoms have been present. In these cases the symptoms are probably due to toxic action. It is still a question whether meningism is an early stage of meningitis. In some cases there seems to be some reason for this assumption, in others not. But up to the present, there is no direct proof of such a transition.

Rhein<sup>6</sup> made post mortem examinations on nine cases of meningitis; seven were diagnosed clinically and pathologically as tuberculous meningitis. One recovered from a tuberculous meningitis, but died one month

2. Rolly: *Deutsch. med. Wchnschr.*, 1911, xxxvii, 774.

3. Wollstein: *AM. JOUR. DIS. CHILD.*, 1911, i, 42.

4. Oseki: *Ziegler's Beitr. z. allg. Pathol.*, 1912, lii, 540.

5. Kirchheim and Schroeder: *Deutsch. Arch. f. klin. Med.*, 1911, ciii, 218.

6. Rhein: *Jour. Am. Med. Assn.*, 1912, lix, 165.



later of a pneumonia. The ninth case was one of pneumococcus meningitis. No tubercle bacilli were found in sections of the meninges and central nervous system. This is perhaps due to the fact that the sections were hardened in Kaiserling's solution. Blood-vessel changes as well as changes in the cortex were present in all. In three there was marked evidence of encephalitis. The author believes it possible, if not probable, that the exudate in the meninges is due to a mixed infection and not alone or at all to the tubercle bacillus. This explains the rapidity of the course, and the fact that in children the pathological lesions of the meninges does not resemble those of tuberculous meningitis occurring in patients succumbing to tuberculosis of other organs. The histologic picture in areas somewhat removed from a tubercle shows a round cell infiltration (simple inflammatory process as described by Villaret and Fixier, Peron, Hayen and Chantemesse). Diffuse infiltration without tuberculous granulations and without definite tubercles were described by Siredey and Tinel. The cellular changes are not typical. Plasma, lymphoid and phagocytic cells occur as in other inflammatory conditions. The vessels show thickening of the arteriole walls and some of the veins. Sometimes the lumina of these are obliterated. There is evidence of perivascular round cell infiltration. In some vessels the coats are thickened and there is cellular proliferation of the intima. Hektoen has described primary endarteritis and phlebitis with thrombosis and obliteration of the veins. The evidence of encephalitis was shown by distention of the perivascular spaces. In three cases there was present marked round cell infiltration of the superficial layers of the cortex. Plasma cells were seen in six cases.

Rhea<sup>7</sup> calls attention to the occurrence of extensive intraspinal hemorrhage in influenzal meningitis. In the brain substance an acute inflammatory reaction may take place about the blood-vessels. To these changes may be attributed some of the permanent lesions of the central nervous system which occasionally follow some of the acute illnesses associated with cerebral symptoms. Bacteriemia may develop in the course of influenzal meningitis. Organization of the exudate may lead to internal hydrocephalus. In chronic meningitis following the acute stage of influenzal meningitis the arteries of the meninges may show varying degrees of increase in connective tissue within the internal elastic membrane. Influenzal meningitis may be followed by paralysis of varying extent.

Davis<sup>8</sup> made post mortems in five of his seven cases of influenzal meningitis. In four there was an abundant highly purulent greenish-yellow exudate. In one case the exudate was less profuse and limited chiefly to the base and vessels of the Sylvian fissure. The exudate was

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7. Rhea: Arch. Int. Med., 1911, viii, 133.

8. Davis: AMER. JOUR. DIS. CHILD., 1911, i, 249.

abundant at the base and about the frontal lobes, leading to flattening of the convolutions. The cortical exudate occurred in large patches and was more abundant along the vessels. In one case, a pseudomembrane was seen along the inner surface of the dura which was red and congested. At the base thick greenish pus was found adherent to the dura. In one case a large subcortical abscess was found containing many bacilli. This abscess penetrated to the lateral ventricle. In the same case, there was softening of the cortex on the other side, but no abscess formation. Hemorrhage in the brain substance was not seen. In one case there was marked acute hydrocephalus. The exudate along the spinal cord was less marked than over the brain. It was more abundant along the posterior surface. Round cell infiltration, especially along the vessels of the substance of the cord, was seen penetrating into the gray matter. Pus was found in the central canal in two cases. Histologically, the exudate was rich in cells. Fibrin was either absent or present in traces only. Three types of cells were seen—polynuclears, mononuclears and large endothelial-like cells. The *Bacillus influenzae* was present in large numbers on the exudate. Small hemorrhages were occasionally seen. The walls of the blood-vessels were infiltrated and thrombosis was not rare. The exudate was situated on the deepest portions of the sulci, and for a short distance along the vessel into the cortex. But in this situation the infiltration was limited to a few polynuclear and plasma cells near the surface.

Acute rhinitis was present in 3 cases. In one there was extensive necrosis of the entire nasal mucosa involving the cribriform plate and downward into the pharynx. Acute bronchitis was present in 4 cases. In 3 cases there was evidence of bronchopneumonia along the posterior portions of the lungs, and more extensive in the lower lobes. The process in the lungs was distinctly lobular with infiltration of the peribronchial lymph channels containing a large number of plasma cells.

The bacilli were found in one case in the turbid peritoneal fluid. In another case there was a fibrinous exudate on the peritoneum and over the spleen originating from a splenic infarct. Acute degeneration of various viscera is not uncommon. In two cases, the bacillus was found in the heart's blood, in another case in the pericardial fluid. In three cases it was found in the bronchial secretion mixed with streptococci. In one case it was recovered from the surface of the nasal mucosa.

In a case of pneumococcus meningitis, which has now become classical, Holt<sup>1</sup> found at autopsy an old meningitis of the convexity in the exudate of which the pneumococcus was found. At the base the meninges were normal. Clinically, a perfectly clear and sterile fluid was found on lumbar puncture.

## BACTERIOLOGY

Martha Wollstein<sup>3</sup> made an extensive study of the *Bacillus influenzae* as seen in influenzal meningitis. It was found to be a slender rod varying greatly in size and staining deeply at the poles. It is Gram-negative. It is invariably hemophilic and its marked characteristic is pleomorphism. The bacilli are usually present in large numbers in the cerebrospinal fluid. It usually occurs free, there being only slight phagocytosis. The organism did not grow on plain agar and sheep serum agar.

A culture of fifteen to twenty-four hours' duration shows minute regular bacilli among which a small number of threads are seen. On the second day, there is an increase in the number of curved forms and the threads are longer. The bacilli also increase in thickness. After seventy-two hours' growth many bizarre forms are seen.

Mice are highly susceptible to peritoneal injection. The peritoneum shows little exudate, the spleen is always swollen, the lungs and kidneys are congested. Bacilli are found in the heart's blood, peritoneum and other organs.

Small guinea-pigs (200 grams in weight) usually die within twelve to twenty-four hours after an intraperitoneal injection of  $\frac{1}{2}$  to 1 culture. There is an increase of peritoneal fluid which is turbid. Phagocytosis is rare. The spleen is two to three times its normal size. The kidneys are congested; likewise the lungs, which show areas of inflammation. The bacilli were found in pure cultures in the heart's blood and viscera. Organisms were also recovered from the surface of the pia of the brain and spinal cord.

Rabbits of 1200 grams weight, when injected in the ear veins, succumbed in fifteen to thirty-six hours. Small hemorrhages were found along the parietal peritoneum, within the serous coat of the intestines, beneath the capsule of the liver and along the pleura. The spleen is swollen and soft; the kidneys are much congested. The lungs showed areas of hemorrhage and inflammation. Positive cultures were obtained from the heart's blood, viscera, urine, surface of the cord and brain, and the mucous membrane of the upper nasal cavities.

The effect on monkeys will be described in the section on experimental meningitis.

Wollstein found all strains of the bacillus derived from cases of influenzal meningitis virulent for small animals, whereas those derived from the respiratory tract are not always so. The bacillus was recovered from the heart's blood in only four of the cases.

The agglutination reaction was found to be unsatisfactory. The determination of the opsonic index was but slightly more satisfactory.



In 1909, Cohen<sup>9</sup> reported several cases of meningitis due to a hemophilic bacillus, closely related to the *Bacillus influenzae*. It apparently differed from the latter organism in that it was highly virulent for rabbits, guinea-pigs and mice. It was present in the blood in all the cases, causing affection of the serous membranes. This observer claimed that it differed from the *Bacillus influenzae* in its agglutination and conglutination reactions. He called the form of meningitis due to this organism *meningite cerebrospinale septicaemique*. Similar cases were observed in France, Belgium, America and England. The same organisms were cultivated in a case of Prosek and Zatelli.<sup>10</sup> It is still a question whether this organism is to be regarded as a distinct species or merely a virulent form of the *Bacillus influenzae*.

#### EXPERIMENTAL MENINGITIS

By injecting through a trephine hole tubercle bacilli of established virulence for guinea-pigs and rabbits, Manwaring<sup>11</sup> succeeded in producing tuberculous meningitis in dogs. The disease was followed by paralysis and death. The effects of injection of suspensions of canine leukocytes were studied by this observer. His results will be described in another section.

Martha Wollstein<sup>12</sup> produced meningitis in monkeys (*Cercopithecus callitrichus* and *Macacus rhesus*) by injecting subdurally a virulent strain of bacillus influenzae. Symptoms usually appeared in five hours; the first evidence of disease being a disinclination to move actively. The cerebrospinal fluid became turbid and contained many bacilli. Death occurred from thirty-six hours to three to four days after inoculation.

Wollstein refers to the experiments of Cantani and Ritchie. Cantani injected influenza bacilli into the brain in rabbits. A non-lethal dose set up a chronic meningitis. Sometimes pus accumulated in the lateral ventricles. A microscopic examination showed an acute encephalitis.

Ritchie inoculated a *Macacus rhesus* with two blood-agar cultures in the lumbar region. The animal died eighteen hours later. At autopsy there was evidence of a beginning meningitis. Preparations from the surface of the cord and brain revealed numerous bacilli.

In Wollstein's animals a purulent exudate was found along the superior longitudinal sinus spreading laterally. There was a turbid exudate over the cord and the base of the brain. The exudate was marked at the site of inoculation. Smears from the pia arachnoid of the brain and cord showed a varying number of bacilli. On section there was seen a purulent leptomeningitis of the cord and the surface and

9. Cohen: Ann. de l'Inst. Pasteur, 1909, xxiii, 273.

10. Prosek and Zatelli: Wien. klin. Wehnschr., 1911.

11. Manwaring: Jour. Exper. Med., 1912, xv, 1.

12. Wollstein: Jour. Exper. Med., 1911, xiv, 73.



sulci of the brain. The exudate occurred chiefly about the blood-vessels. Innumerable bacilli were found among the pus cells. In one animal an influenzal empyema was found at the base of both lungs.

#### MENINGISM

Sachs<sup>13</sup> observed 16 cases of meningism amongst 400 cases of scarlet; 11 times it occurred in children 8 to 13 years of age; 3 times in children 2, 4 and 5 years of age, respectively. The condition was also twice found in adults. The most frequent symptoms were rigidity of the neck, hyperesthesia, change in mental condition and Kernig's sign. The Kernig sign persisted during the early period of convalescence. In one-half of the cases there was an increase of pressure in the cerebrospinal system, but there was no increase in albumin or abnormality in the sediment of the cerebrospinal fluid. The prognosis of meningism is always good and lumbar puncture seems to relieve the condition.

In cases of otitis, Schwartz<sup>14</sup> has at times observed stupor, continuous delirium and myosis. Immediate relief of these symptoms followed paracentesis of the inflamed drum. Schwartz refers to a case of Hicks where mydriasis, ptosis and paresis of one leg were completely relieved by tympanic paracentesis. Oppenheim, in his book, calls attention to the fact that a purulent otitis may be accompanied, especially in childhood, by brain symptoms resembling those of meningitis such as headache, vertigo, stupor, delirium and general convulsions. Even optic neuritis and paralysis of the abductus have been observed.

#### MENINGITIS SEROSA

Boenninghaus, in 1897, first drew attention to this condition as one of the intracranial complications of middle ear disease. Wagener observes that the symptoms may be latent. In marked cases the following symptoms may be present: headache, general malaise, vomiting, rigidity of the neck, Kernig sign, nystagmus, irregularity of pupils and increased tension of the pulse. One of the most constant symptoms is to be found in the fundus. In the mildest cases it may manifest itself as a unilateral hyperemia of the papilla and venous stasis. In the severe cases papillitis, choked disk and retinal hemorrhages are frequently seen. Wagener never observed primary optic atrophy.

#### TUBERCULOUS MENINGITIS

According to Holt,<sup>1</sup> the average duration of the disease after the onset of definite symptoms is two and a half weeks. Most of his patients had previously been in apparently good health. The v. Pirquet reaction was positive in 51 out of 65 patients. In 11 it was negative, and in 3

13. Sachs: *Jahrb. f. Kinderh.*, 1911, lxxiii, Suppl., 68.

14. Schwartz: *Arch. f. Ohrenh.*, 1910, lxxxi, 77.

doubtful. Of these 14, four were moribund, and 7 extremely prostrated at the time the test was performed.

Riva-Rocci<sup>15</sup> observed four cases of tuberculous meningitis in children, 2½ years of age, that suffered from tympanites throughout the whole course of the disease. In two of these, there was found at autopsy an acute miliary tuberculosis of the peritoneum. In view of these findings, the author thinks that the presence of tympanites in tuberculous meningitis should lead us to suspect the existence of tuberculous peritonitis.

In infancy, Morse<sup>16</sup> has often observed an acute onset. The symptoms of spinal and cerebral irritation are less marked in this form of meningitis. It is rarely observed below 3 months of age. At this period of life, tuberculous meningitis runs an irregular course. Symptoms of irritation may be wholly absent. On the other hand, general flaccidity and diminished or absent reflexes are often observed. The duration is short. Morse has observed one case of only thirty-six hours duration. In infancy, remission of symptoms is less frequently seen than in later childhood.

Laparicinade<sup>17</sup> calls attention to the frequency of occurrence of tuberculous meningitis in infants below 2 years of age. Amongst forty-two cases collected from the literature not previously published, upwards of one-half were under 2 years of age. Three types of this disease are observed in suckling infants: eclamptic, hemiplegic and somnolent. In the eclamptic type, we observe after an initial convulsive seizure a rise of temperature, stiffness of the neck, more or less paralysis of hemiplegic or paraplegic form, followed by partial or general convulsions. Death usually occurs in two or three days during a convulsive seizure.

Hemiplegic form: An infant suffering from slight fever, develops more or less complete paralysis of one side of the body. Localized or general convulsions, stiffness of the neck and bulging of the fontanelle appear. The infant gradually falls into coma.

Somnolent form: This form is characterized by four cardinal symptoms: Progressive somnolence, ocular catalepsy, progressive emaciation, instability and irregularity of the pulse. The somnolence is progressive. At first the infant is taciturn, moody and depressed. It falls into normal sleep four or five times a day. At a later period the infant awakes only for drink. Ultimately deep coma develops.

Ocular catalepsy (fixity of gaze) is due to absence of winking. With it there is associated amblyopia and absence of conjunctival reflex. The infants sleep with wide open eyes, which have a vacant expression.

15. Riva-Rocci: *Riv. di. clin. pediat.*, 1911, ix, 758.

16. Morse: *Brit. Med. and Surg. Jour.*, 1911, i, 701.

17. Laparicinade: *Med. Press and Circ.*, 1911, N. S., xci, 414.

The emaciation begins during the prodromal period. At the onset of the disease the only observable abnormality may be an instability of the pulse. The pulse may vary within short intervals, from 80 to 160. Vomiting and diarrhea, when present, are but slightly amenable to treatment.

When the disease is fully developed, the infant presents a characteristic picture. It usually lies on the back with wide-open, staring eyes. Conjunctivitis is a frequent complication. The temperature is usually subfebrile.

#### INFLUENZAL MENINGITIS

Among the 197 cases, Holt<sup>1</sup> observed four of influenzal meningitis, all of which were fatal. In 3 of the 4 cases, the organism was obtained from the bronchial secretion during life and in 2 from the nasopharynx. In 3, all those examined, it was found in the blood. In one case the *Bacillus influenzae* was found in the pus from an abscess of the elbow. A fatal influenzal meningitis developed later.

According to Pisek,<sup>18</sup> influenzal meningitis is characterized by severe constitutional symptoms which are out of proportion to the temperature curve. In this form of meningitis there is a rather sudden transition from symptoms of cerebral congestion to those due to intraventricular and subarachnoid pressure. Headache suddenly becomes more intense and there is pain on pressure over the eyes and supraorbital region. There is at first restlessness which is due to irritation of the sensory centers; later there is depression or abolition of the reflexes as a result of pressure. Convulsions may occur at the onset or paroxysmally during the course of the disease. There are usually present retraction and rigidity and slight opisthotonus. At this time there may exist an influenzal pneumonia, mild peritoneal irritation or involvement of the accessory nasal sinus. Albuminuria occurs in 0.6 per cent. At first there is tachycardia or arrhythmia. Later the pulse is continuously high. There is steady emaciation. There may be delirium, stupor or profound coma. Severe convulsive seizures may occur at the beginning. Photophobia is often present. Other symptoms observed are irregularity of the pupils, loss of pupillary light reflex, nystagmus and neuroretinitis. The respirations vary with the stage of the disease and the condition of the patient. It is increased with high fever, sighing and shallow with stupor, irregular with coma. Cheyne-Stokes respiration is seen occasionally. The cerebrospinal fluid is uniformly cloudy, with a well-marked straw-colored sediment which shows a predominance of polynuclears and intra- and extra-cellular organisms.

Influenzal meningitis, according to Davis,<sup>8</sup> occurs sporadically, and there is no marked association with epidemics of influenza (la grippe).

18. Pisek: Am. Med., 1912, N. S. vii, 209.



It is confined largely to children under 1 year of age. The first authentic case in the literature was that of Pfuhl in 1892. Since then a large number of observers have reported on this disease, among them being Fraenkel, Ghon, Dubois, Adams, Cohoe, Cohen, Davis and Wollstein. Davis' report is based on seven cases, all of which were fatal. The duration of the disease varied from three to fourteen days. The youngest patient was 5 days of age, the oldest 13 months. There was a definite history of previous "colds" in four cases. The onset was indefinite, the early symptoms being cough, harsh breath sounds or definite signs of pneumonia. Eye symptoms were usually present as well as marked rigidity of the neck and retraction of the head. Definite convulsions were present in five cases. In all the children there was bulging of the anterior fontanel. In only one case was there herpes labialis. Some petechial hemorrhages were seen in one case just before death. The temperature varied from normal to 105 F. or higher, being subject to sudden change. The pulse was irregular, but rapid, 130 to 160. Apparently the period of incubation is not over five days, as two patients (twins) became ill within five days after birth. Lumbar puncture was performed on four patients. Cerebrospinal fluid was turbid, under high pressure and contained many leukocytes, 60 to 80 per cent. of which were polynuclears. The remaining cells consisted chiefly of small mononuclears. Endothelial cells were common. Red blood-cells were either absent or present in very small numbers. Fibrin was scant.

In one case the portal of entry was undoubtedly the nasal cavity as the infection could be traced through the necrotic cribriform plate of the ethmoid. In another case the bacillus was found in large numbers on the inflamed nasal mucosa. In two cases the infection probably originated in the upper respiratory tract.

Brem and Zeiler<sup>19</sup> observed two cases of influenzal meningitis which were treated with hexamethylenamin. The first case simulated an anterior poliomyelitis. There was no retraction of the head or marked stiffness of the neck. The Kernig sign appeared only one day before death. The Babinski was present from the first. Urotropin was given in 5-grain doses by intramuscular injection and 5 grains by rectum every four hours. Its presence in the spinal fluid was demonstrated by Herber's test. There was no apparent effect on the disease. In the second case meningeal symptoms did not appear until the sixth day of the disease. Five-grain doses of urotropin were given by intramuscular injection every four hours. Its presence could be demonstrated by the phenylhydrazin hydrochlorid test in cerebrospinal fluid diluted twenty times. By colorimetric test it was demonstrated in the cerebrospinal fluid in the strength of 1 to 3,750, in the urine in the strength of 1 to

19. Brem and Zeiler: *AM. JOUR. DIS. CHILD.*, 1911, i.



1,000. Hemoglobin appeared in the urine. Permanent drainage by means of a needle in the spine led to a fall of the temperature to normal. It remained so for twenty-four hours, until the needle worked out. There was no apparent effect from the administration of urotropin.

According to Leichtenstern,<sup>20</sup> influenzal meningitis usually appears at the height or rather at the beginning as a fulminating meningitis. The symptoms vary accordingly as it affects the convexity or the base of the brain. In the former case, which is the usual condition, there are intense headaches, absence of the rigidity of the neck and early loss of consciousness. When the base is affected the clinical picture closely resembles that of epidemic cerebrospinal meningitis, including herpes labialis.

#### PNEUMOCOCCUS MENINGITIS

Holt<sup>1</sup> reports on a very instructive case on a baby 20 months of age. There were fever, repeated convulsions and a leukocyte count of 24,000; there was no rigidity of the neck or extremities. Lumbar puncture on the first and seventh days yielded a perfectly clear fluid, showing no organisms on smears or cultures. During the third week, the child developed pneumonia with distinct signs of consolidation. On the third puncture, at this time 105 c.c. of fluid were removed, which again was negative. After the lapse of six weeks there were no active symptoms, but there was wasting and defective mentality. Death occurred in the eleventh week from a second attack of pneumonia. At autopsy there was found an old meningitis at the convexity in the exudate of which pneumococci were demonstrated. In eight of twenty-two of Holt's cases, the duration of the disease was three days or less. In two-thirds of his cases it was six days or less. The diagnosis of this form of meningitis presents great difficulties, as the lesions are occasionally localized at the convexity. As a result of this localization such characteristic symptoms as opisthotonos, irregularity of the pulse and respirations, distention of the fontanel and involvement of the cranial nerves may be absent. Pneumococcus meningitis occurs in younger children than either epidemics of cerebrospinal meningitis or tuberculous meningitis. One-half of Holt's cases were under 6 months of age, two-thirds of them under 9 months.

According to Schlesinger,<sup>21</sup> pneumococcus meningitis may have either an apoplectic, acute, subacute or insidious course. The fever in favorable cases is less high and of shorter duration than in epidemic cerebrospinal meningitis. Rapid euphoria appears after cessation of fever, despite the persistence of meningitic symptoms.

21. Schlesinger: *Wien. med. Wchnschr.*, 1911. lxi. 40.

20. Leichtenstern and Stricker: *Influenza*, Wien and Leipsic, 1912.

According to Rolly,<sup>2</sup> the mode of invasion of meningococcus meningitis is dependent on the portal of entry; 8 of his 30 cases began with or after a pneumonia or bronchitis; 6 with sepsis and endocarditis; 3 with otitis media; 9 with rhinitis or disease of the accessory sinus, 1 after trauma. In 3 cases the cause was unknown. In the 26 fatal cases, the disease began with slight prodromata, lasting one to seven days. These consisted of headache, backache, general malaise, anorexia, dizziness and occasional vomiting. In 5 cases no premonitory symptoms were present, but the disease began with fever, vomiting, agonizing headache and marked vertigo. Only once was a chill present. Rigidity as well as pain on moving the head was constant. The Kernig sign was pronounced. Herpes was rather unusual. The cases exhibited marked restlessness and early loss of consciousness. In 3 cases clear cerebrospinal fluid was obtained in which pneumococci were seen. The duration of the disease varied from two to twenty-five days.

#### OTHER SUPPURATIVE MENINGITIDES

Two cases of meningitis due to *Bacillus coli* were observed by Holt.<sup>1</sup> The first was a baby 4 weeks of age, which was admitted to the hospital with Erb's palsy and malnutrition. During its stay it developed the usual symptoms of meningitis with a temperature up to 103, general hyperesthesia and rigidity and a leukocyte count of 13,000. The disease ended fatally after ten days' illness. The second infant was also 4 weeks of age; there was a previous history of *Bacillus coli* infection of the urinary tract. The patient recovered from the acute symptoms, but developed a secondary hydrocephalus. A case of typhoid meningitis was observed by David and Speik.<sup>22</sup> One due to paratyphus infection by Boonacker and Gorter. One of infection by the Friedlander bacillus by Guinon and Simon<sup>23</sup> (recovery in four days). Of ten cases of pyogenic (staphylococcus or streptococcus) form, six were seen by Holt in newborn babies. In five cases, the meningitis was secondary to spina bifida. In one the meningitis followed an operation for hydrocephalus. In only two was the meningitis apparently primary clinically, the development was rather rapid, being accompanied by severe general and local symptoms. The termination was always unfavorable. Only once did a meningitis follow an otitis or its complications. This was in a 15-months-old child on whom a double mastoid operation was performed, in Europe. The dressing was unchanged for nearly two weeks; that is, during the trip across the ocean. The discharge was very foul and the wound in bad condition. At autopsy, however, there was found no connection between the mastoid and the meninges. The meningitis was of the tuberculous variety.

22. David and Speik: Jour. Am. Med. Assn., 1911, lvi, 882.

23. Guinon and Simon: Bull. et mem. Soc. d. hôp. de Paris, 1910.

Remlinger<sup>24</sup> describes cases of aseptic meningitis in which there was turbid or purulent fluid without any organisms being demonstrable.

#### DIAGNOSIS

Lucas<sup>25</sup> gives a detailed discussion of the diagnostic value of the cerebrospinal fluid in various cerebral affections. He shows that the cytology in tuberculous meningitis is not characteristic, as a similar picture is seen in a number of cerebral affections, such as encephalitis, myelo-encephalitic meningism, syphilis of the meninges and anterior poliomyelitis. In myelo-encephalitis, both experimental and human, the cerebrospinal fluid was turbid, contained fibrin and showed a large number of mononuclear cells or lymphocytes. In 248 cases of tuberculous meningitis, the amount of fluid varied from 5 to 120 c.c. In some cases it was clear, in others opalescent. Occasionally the fluid was turbid. There was no clot formation in a little over 10 per cent. But it was present some time or other in every case. The number of cells per cubic millimeter varied from 14 to 920, the average being 206. Fifty per cent. of the cases had 100 cells or below. The differential count showed a variation from 100 per cent. lymphocytes and mononuclears to 89 per cent. polynuclears. In twenty-five instances the polynuclears numbered 30 per cent. or over.

In 102 cases of pyogenic meningitis the amount of fluid varied from a few drops to 250 c.c. In three cases the fluid was clear. Clot formation was always present, except in clear fluid; the number of cells varied from forty-five to 2,600 per cubic millimeter. There was always a preponderance of polynuclears. In chronic cases the mononuclears equalled or were in excess of the polynuclears. The cytology alone is therefore not sufficient for the separation of the various forms of meningitis.

The diagnosis of tuberculous meningitis rests, according to Dunn,<sup>26</sup> on a triple basis, namely, clinical character, examination of the cerebrospinal fluid, and the invariably fatal termination. No one of the characteristic symptoms and signs is invariably present. The onset may be sudden or gradual; the temperature high, moderate or low. Unconsciousness may appear rapidly during the early stages or slowly and at a late period. The following symptoms may be present or absent: headache, rigidity of the neck, Kernig sign, localizing neurological signs, convulsions, vomiting and leukocytosis.

The characteristics of the cerebrospinal fluid are of greater value than the clinical picture. In sixty cases which the author analyzed, a predominance of lymphocytes was constantly present. But such a lymphocytosis may be present in other conditions. Determination of the number

24. Remlinger: *Gaz. d. hôp.*, 1911, lxxxiv, 1125.

25. Lucas: *AM. JOUR. DIS. CHILD.*, 1911, i, 230.

26. Dunn: *Arch. Pediat.*, 1910, xxvii, 685.



of cells by the centrifuge is an inaccurate method. The author advises that the number of cells should be estimated by the use of the white blood counting pipet. The staining mixture given below is drawn up to the 0.5 mark of the white blood counter, the fresh cerebrospinal fluid is drawn up to the 11 mark. The ordinary blood counting slide is used. The number of cells counted on ten slides represents the number of cells per cubic millimeter. The staining mixture used is as follows:

	Gm. or C.C.
Methylene violet .....	0.1
Acetic acid .....	2.0
Water .....	50.0

Glacial acetic acid alone may be used. The number of cells found in normal fluid by this method varies from none to three cells per cubic millimeter. Ten cells, however, are taken by the author as the limit of a normal count.

In 60 cases of tuberculous meningitis, representing 71 examinations, there was a count above normal in all cases. The lowest count was 30, the highest 920. In the following conditions the cell count was normal—lobar pneumonia, anterior poliomyelitis, typhoid, solitary tubercle, cerebellar tumor, cerebral hemorrhage, rheumatic fever, otitis media, measles with pneumonia, gastro-enteric intoxication. In one case of tetanus there was a cell count of 60. The cell count is of special value in the differentiation between tuberculous meningitis and cases of gastro-enteric disturbance and toxic absorption. The author did not find any definite relation between the stage of the disease and the number of lymphocytes.

Hemenway<sup>27</sup> found tubercle bacilli in the cerebrospinal fluid in 135 out of 137 cases. In one of the negative cases only 2 cubic centimeters of fluid were obtained; in the other the fluid was withdrawn at an early stage of the disease. The technic of the author is as follows:

The cerebrospinal fluid is collected in several test-tubes, about 20 c.c. in each tube. The last fluid after the child is set up is the most important. The tube should not be shaken as the fibrin film or coagulum forms more readily when the tube is not disturbed. The tubes are placed in the incubator; after ten hours the film can be removed entire with a platinum loop. It is then spread out carefully with fine needles on a glass slide. It is then fixed and stained by Sabbet's method.

In about 40 per cent. of the cases no coagulum forms. In these cases the sides of the test-tube are scraped with the platinum loop and any material removed is superimposed drop by drop over a small area on a glass slide. Each drop is dried in the air and fixed in the flame before another is added. The sediment from the test-tube may be superimposed by means of a fine capillary tube in the same manner. If no coagulum forms and no tubercle bacilli are found in the first puncture fluid, the needle on the second puncture, just before being withdrawn, is pushed slightly forward so as to touch the anterior surface and

27. Hemenway: AM. JOUR. DIS. CHILD., 1911, i, 37.



1 or 2 drops of blood are allowed to flow in the last tube. This aids in the formation of a coagulum. The tubercle bacilli are more numerous at a late stage of the disease.

Netter and Gendron,<sup>28</sup> in their observation on the cytodagnosis of tuberculous meningitis, find that in childhood there is an average of 100 lymphocytes to the cubic millimeter. In poliomyelitis there are about twenty lymphocytes to the cubic millimeter and in other meningeal conditions three to fifteen lymphocytes per cubic millimeter.

In acute meningitis and in progressive paralysis, Weil and Kapka<sup>29</sup> found the meninges permeable to sheep hemolysins. In acute meningitis, the total hemolysin (amboceptor and complement) is demonstrable. The degree of reaction depends but slightly on the varying degrees of permeability of the meningeal vessels, but rather on the abundance of hemolysins in the blood.

Strouse<sup>30</sup> finds the Noguchi reaction (butyric acid reaction) positive in all meningitis cases. It was negative in three cases of meningism.

Trembur<sup>31</sup> found that incubation of the cerebrospinal fluid in sealed test-tubes at 37° F. for twenty-four to seventy-two hours, greatly increases the number of tubercle bacilli.

Tinel and Gastinel<sup>32</sup> describe a number of meningeal states in tuberculosis. In one group the patient suffers from attacks of headache every evening. There are in addition slight vomiting, rigidity, Kernig and transitory changes in pulse and temperature. Lumbar puncture, which relieves the symptoms, immediately yields a cerebrospinal fluid, which, though usually normal, occasionally shows a slight increase in albumin and lymphocytes; no tubercle bacilli are found.

In another group, there are in addition to the above symptoms, sciatic pain, which is due to anatomical changes in the nerve, as a healed tubercle or cyst.

In a third group, the intensity of the symptoms leads one to suspect tuberculous meningitis, but the condition gradually improves. There may be several attacks of gradually lessening severity. The cerebrospinal fluid shows moderate lymphocytosis, but it may be entirely negative. At autopsy, there is found a diffuse sclerosis of the meninges without signs of recent inflammation.

#### PROGNOSIS

Undoubted cases of recovery from tuberculous meningitis have been recorded in the literature by a number of observers, amongst these being Freyhan, Henkel, Barter, Gross, Claisse and Abrami, Riebold, Rumpel.

28. Netter and Gendron: *Bull. Soc. de pédiat. de Paris*, 1911, p. 226.

29. Weil and Kapka: *Med. Klin.*, 1911, vii, 1314.

30. Strouse: *Jour. Am. Med. Assn.*, 1911, lvi, 1171.

31. Trembur: *Klin. Jahrb.*, 1911, xxiv, 359.

32. Tinel and Gastinel: *Rev. de méd.*, 1912, xxxii, 4, 241.

Stark, Archangelsky, Hochstetter and Dunn. These observers found the tubercle bacilli in the cerebrospinal fluid.

Autopsy evidence of a previously existent tuberculous meningitis have been found by Jannssen, Thomalla, Weermann and Leube.

Cases of recovery from pneumococcus meningitis are recorded by Jemma, Hauer, Kohts (two cases), Grober, Schlesinger<sup>21</sup> and Rolly.<sup>2</sup>

#### TREATMENT

Martha Wollstein<sup>12</sup> succeeded in immunizing a goat with bacillus influenzae. The blood acquired moderate agglutinating and high opsonic power. Injected in the spine it arrested the progress of the experimental meningitis and brought about recovery. As a result of the injection of the serum, the bacilli were more freely engulfed by the phagocytes. The number of the organisms became reduced, their capacity for growth diminished, and their entrance into the blood arrested. This led to a cessation of the local inflammatory process and progressive amelioration of the symptoms. At first, the serum was injected after one hour's inoculation of the bacilli. Later successful results were obtained even when the serum was applied twenty-four hours later.

Manwaring<sup>11</sup> inoculated dogs subdurally with tubercle bacilli of established virulence for guinea-pigs and rabbits, and succeeded in producing a tuberculous meningitis. The disease was followed by paralysis and death. When suspension of canine leukocytes was injected subdurally, the onset of the paralysis was delayed, and the life of the animal was prolonged. With large doses of tubercle bacilli, the injection of leukocytes had no effect. With small numbers of very virulent bovine bacilli, the leukocytes uniformly produced a prolongation of the latent period. But they had a less evident effect on the subsequent course of the disease. All the animals died.

With small doses of less virulent human bacilli, half of the animals did not develop paralysis. The others developed paralysis after a much prolonged incubation period, from which one animal died. In some of the treated dogs, the tuberculous lesions in the upper part of the subdural space had apparently been arrested or caused to undergo resolution. In the lower third of the spinal cord, the lesions persisted or advanced to a chronic condition.

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# INDEX TO CURRENT PEDIATRIC LITERATURE

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## ANATOMY AND PHYSIOLOGY

- Calcium Content of the Blood in Children by Wright's Method, Determination of.—M. Katzenellenbogen.  
Ztschr. f. Kinderh., 1913, viii.

## BACTERIOLOGY AND PATHOLOGY

- Achondroplasia, Study of.—Bertolotti.  
Presse méd., June 28, 1913.  
Hypophysis, Obesity as Result of a Basophil Adenoma in the.—T. Bauer and H. Wassing.  
Wien. klin. Wchnschr., July 24, 1913.  
Status Thymico-Lymphaticus Among Filipinos.—B. C. Crowell.  
Philippine Jour. Sc., April, 1913.

## HYGIENE

- Bathing the New-Born Infant, Technic for.—F. Weisswange.  
Zentralbl. f. Chir., July 26, 1913.  
Infant Welfare Stations.—O. Reinach.  
München. med. Wchnschr., June 24, 1913.  
Milk Supply of City, Relation of Infected Stream to.—F. M. Meader.  
New York State Jour. Med., July, 1913.

## METABOLISM AND NUTRITION

- Feeding, Albumin-Cream Milk in Infant.—E. Feer.  
Jahrb. f. Kinderh., 1913, lxxvii.  
Feeding of Infants, Breast.—E. G. A. Webb.  
Med. Press and Circular, July 2, 1913.  
Feeding of Infants, Some Mooted Points on.—J. D. Love.  
South. Med. Jour., Nashville, July, 1913.  
Feeding, Science of Infant.—S. Engel.  
Deutsch. med. Wchnschr., June 26, 1913.  
Food for Babies.—M. A. Asserson.  
New York Med. Jour., July 26, 1913.  
Lipins in Diet During Growth, Necessity of Certain.—E. V. McCollum and M. Davis.  
Jour. Biol. Chem., Baltimore, July, 1913.  
Metabolism in an Atrophic Infant.—K. Frank and G. Wolff.  
Jahrb. f. Kinderh., 1913, lxxvii.  
Metabolism in Dyspepsia and Intestinal Intoxication.—I. Jundell.  
Ztschr. f. Kinderh., 1913, viii.  
Milk for Infant Feeding, the Backhaus Method of Preparing.—A. Backhaus.  
Berl. klin. Wchnschr., July 21, 1913.  
Milk, The Iso-Electric Points of Human, and Milk of Various Animals.—A. Yippo.  
Ztschr. f. Kinderh., 1913, viii.  
Nourishment of Infants.—C. S. Ordway.  
Ohio State Med. Jour., July, 1913.  
Nutrition, Hitherto Overlooked Factors in.—H. Schaumann.  
Med. Klin., July 13, 1913.  
Rachitis, Hypophysis Treatment in: Sixteen Cases.—K. Weiss.  
Therap. Monatsh., July, 1913.

Rachitis and Its Relation to Development of the Chest.—E. Zeltner.  
Jahrb. f. Kinderh., 1913, lxxvii.

Whey and Digestive Ferments.—H. Davidsohn.  
Ztschr. f. Kinderh., 1913, viii, No. 2.

### TUBERCULOSIS AND SYPHILIS

Heliotherapy in Surgical Tuberculosis.—M. Jerusalem.  
Wien. klin. Wchnschr., July 17, 1913.

Lupus Erythematosus, Efficacy of Carbon Dioxid Snow in Treatment of.—  
P. Haslund.  
Hospitalstid., July 23, 1913.

Meningitis, Recovery from Tuberculosis; two Cases.—V. Reichmann and F. Rauch.  
München. med. Wchnschr., July 1, 1913.

Pott's Disease, Transplantation of a Portion of the Tibia to the Spine for.—  
F. V. Albee.

Rev. de chir., July, 1913.

Spine, Treatment of Pott's Disease of.—G. B. Packard.  
Colorado Med., July, 1913.

Syphilis Among School Children.—H. H. Hazen.  
Washington Med. Ann., July, 1913.

Congenital Syphilis of Small Intestine, with Spirochetes, Histology of.—G.  
Warstat.

Virchows Arch. f. path. Anat., May, 1913.

Syphilis, Prophylaxis of Hereditary.—A. Gallico.  
Policlinico, Rome, July 13, 1913.

Syphilis, Serodiagnosis of Inherited.—S. Samelson.  
Ztschr. f. Kinderh., 1913, viii, No. 2.

Tuberculin Reaction in Children.—L. Jeanneret.

Rev. med. de la Suisse romande, June 20, 1913.

Tuberculosis, Albumin Reaction in Sputum in Diagnosis of.—H. Schmitz.  
Med. Klin., July 20, 1913.

Tuberculosis, Compulsory Declaration of.—F. Maffi.  
Gazz. d. osp., July 1, 1913.

Tuberculosis, Further Measures for the Campaign Against.—J. Landsberger.  
Berl. klin. Wchnschr., July 21, 1913.

Tuberculosis in Infants, Pulmonary.—A. v. Korschegg and R. Lederer.  
Monatschr. f. Kinderh., 1913, xii, No. 3.

Tuberculosis in Children, Surgical, with Method of Treatment.—A. H. Tubby.  
Lancet, London, July 19, 1913.

Tuberculosis, in Children Treated with Mixed Bacterins, Clinical Reports of Ten  
Cases of Pulmonary.—L. C. Ager.

New York State Jour. Med., July, 1913.

Tuberculosis in Infants and Young Children, Treatment and Prognosis of.—  
M. Hollensen.

Beitr. z. Klin. d. Tuberk., 1913, xxvii, 1.

Tuberculosis of the Skin.—J. Jadassohn.  
Med. Klin., July 20, 1913.

Tuberculosis, Operative Treatment of Peritoneal and Genital.—O. Schmidt.  
Ztschr. f. Geburtsh. u. Gynäk., 1913, lxxiii, No. 2.

Tuberculosis, Pulmonary, and Northern Seashore.—Ide.  
Med. Klin., July 13, 1913.

Tuberculosis, Renal, in Three Girls.—J. Oraison.  
Jour. d'Urol., July, 1913.

Tuberculosis, The Children of the.—W. Weinberg.  
Deutsch. med. Wchnschr., July 10, 1913.

Tuberculosis, Toxic Action of Aberrant Bile in Pulmonary.—P. Serph, A. and A.  
Many.

Semana méd., June 19, 1913.



Tuberculosis, Vaccination Against.—E. Maragliano.  
Riforma med., June 28, 1913.

## ACUTE INFECTIOUS DISEASES

Is Chorea the Result of a Mild, Curable Encephalitis?—Delearde, Valette and J. Comby.

Arch. de méd. des enf., July, 1913.

Diphtheria, Antitoxin in.—J. R. Culkin.

New York State Jour. Med., July, 1913.

Diphtheria Bacillus Carriers, Treatment of with Bouillon Cultures of Staphylococcus Pyogenes Aureus.—J. D. Rolleston.

Brit. Jour. Child. Dis., July, 1913.

Diphtheria Bacilli, Improved Bile Technic for Detection of.—W. V. Drigalski and Bierast.

Deutsch. med. Wehnschr., June 26, 1913.

Diphtheria Chronic, Nasal.—C. M. Miller.

South. Med. Jour., Nashville, July, 1913.

Diphtheria, Cutaneous.—H. Kleinschmidt.

München. med. Wehnschr., July 8, 1913.

Diphtheria, Treatment of.—T. Pontano.

Policlinico, June 22, 1913.

Diplococcus Intracellularis Meningitidis, Isolation of, from Case of Cerebrospinal Meningitis in Native of Philippines.—D. G. Willets and O. Schobl.

Philippines Jour. Sc., April, 1913.

Erythema of Scarlet Fever and That of German Measles, Differentiation of. Diagnosis.—S. D. Hubbard.

Med. Rec., New York, August 2, 1913.

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# American Journal of Diseases of Children

VOL. 6

OCTOBER, 1913

No. 4

## THE CELL CONTENT OF MILK

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The uncertainty of the meaning of the cellular content in milk is apparently either a measure of the lack of differentiation of the cells occurring normally or abnormally in cow's milk, or it would seem to us, due to defective technic in the differentiation of those cells. The latter is shown by those laboratory workers who, while they believe in the smear method of examining milk, yet by failure to employ a differential stain, miss the point at issue. The latter has been demonstrated to us by the use of gentian-violet alone. In a previous article,<sup>1</sup> we have shown that differentiation by any blood-stain such as the one we were using at the time, a 1 per cent. eosin methyl-alcohol followed by a 1 per cent. methylene blue methyl-alcohol, or its counterpart, the Jenner stain, or again the latter modifications of that stain, the Wright, and the one we are now using entirely, the Hastings stain, gives us a picture with sharp differentiation. The interpretation of that picture is one more of experience than of judgment, as we have already shown. That it is a measure of the lack of differentiation is shown frequently by the type of the article discussing this most important subject. A recent one,<sup>2</sup> like the majority of those which appear in print, is not apparently from a laboratory worker who has been trained along these lines, but by a thesis writer who deduces wide conclusions from a small amount of data.

In direct criticism of this article as a typical one of the class of which we speak, we would call attention to certain statements made. While agreeing that "some of the cells found in milk are leukocytes," the writer also states that it is by no means certain that some of them are not epithelial cells. Without attempting to differentiate these types of cells, with examination of samples from 50 cows, the cell content ranging from 4,000 to 3,576,000, the conclusion is deduced that the "formation of the cells, or leukocytes, is a normal function of milk production." This conclusion is verified as claimed, by physical examination of the cows, showing an absence of cow troubles. The fallacy lies in the fact, as we

1. Ross, H. E.: *Jour. Infect. Dis.*, 1912, x, 7.

2. Lewis, D. M.: *Jour. Am. Pub. Health Assn.*, 1911, p. 778.

have stated, that leukocytes constitute only part of the cellular content of milk. One may find the following cells present in the milk sediment when stained with any blood-stain: Epithelial or endothelial cells, varying sized mononuclear cells with basic granule content; polymorphonuclear neutrophils, free or clumped; eosinophils; lymphocytes, so-called because they are the exact analogue of the human lymphocyte; red blood-corpuscles. A study of the illustrations in the accompanying plate made for us by Mr. Kellner of the Yale Clinical Laboratory, shows well these types of cells. It is a lax, but universal, way of terming leukocytes as pus cells and meaning only polymorphonuclear neutrophils. The lymphocyte, while a leukocyte, we have not included in the terminology of pus cells, restricting the latter to polymorphonuclear neutrophils and eosinophils. The difference of staining qualities of the pus cell is well shown in the contrast between Illustrations 1 and 2. The former was from an older milk, and the pus cells were so piled up that it was impossible to make an accurate count. The latter illustration was from a fresh milk in which the pus cells are well differentiated. Illustration 1 shows also a number of epithelial cells and a few lymphocytes, while No. 2 shows no other cells than the pus cells. Illustration 3 shows epithelial and lymphocytes predominating, rarely a free pus cell. As we have previously stated, we have never traced cow trouble to sediment smears similar to the latter, nor have we ever seen the characteristic long chain streptococci accompanying such cellular content. Such a cellular content is common and may easily be the explanation of why there may be 3,576,000 cells in milk samples, and yet physical examination of the milk show nothing. The cellular content of the milk represented by Illustration 2 was approximately 440,000, while that of Illustration 3 was approximately 1,000,000; the former milk was from a herd in which one cow had an infected quarter; the latter showed no herd troubles. In a previous paper, we have stated that there can be no standard for cellular content; we more frequently find milk samples containing 50,000 pus cells to the cubic centimeter, but these pus cells clumped, than we do those in which the content is millions or uncountable, both accompanied by long chain streptococci. We find the former are dependent on parturition or lesser inflammatory troubles of single quarters, while the latter are true garget. We have not pictured samples showing red blood-corpuscles, as these are very obvious, and where in any number not accountable for by pus content, mean cows milked too soon after parturition. Here again, in a minor number of cases, is the lack of a correct stain an error in interpretation of the smear.

We have evidence to show that no major or minor cow troubles ever give an epithelial or lymphocytic cell content apart from clumped pus cells, and would recommend that pus content of milk as generally spoken

of, should mean polymorphonuclear neutrophilic or eosinophilic cells; and further, only when these cells are clumped and in whatsoever numbers. In practically every instance in which streptococci are not found, the characteristic chains may be demonstrated after incubation of the specimen, or when a sample from the cow direct is obtained.

Although, as we have stated, counts of cells from milk samples may range from a few thousand to millions, and on the basis of what has gone before, be corroborated by lack of physical findings of cow disorders, because of the absence of differential counts on the individual cows in the criticized article, we collected the following data after the appearance of that article. For the added reason that generally we are dealing with market milk representing single or numerous herds, we give data from both individual cows and from market samples. We would again state that we use the original Stewart method of centrifugalizing 1 cubic centimeter of milk for ten minutes, rubbing up the sediment over an area approximately 1 square centimeter, and staining with Hastings blood-stain. Each oil immersion field represents 1/4400 part of a cubic centimeter, and we average at least twelve fields.

TABLE 1. SUMMARY OF EXAMINATION OF MILK OF INDIVIDUAL COWS AND SAMPLES OF MARKET MILK

	Individual Cows, 88 Samples	Market Milk, 108 Samples
Samples showing no cell content per average field.....	20	42
Samples showing less than 5 epithelial cells per average field.....	31	36
Samples showing less than 10 epithelial cells per average field.....	5	1
Samples showing 10 to 50 epithelial cells per average field.....	2	0
Samples showing less than 5 epithelial and pus cells per av. field..	7	19
Samples showing less than 10 epithelial and pus cells per av. field..	2	6
Samples showing less than 15 epithelial and pus cells per av. field..	1	1
Samples showing less than 5 free pus cells per average field.....	0	0
Samples showing less than 10 free pus cells per average field.....	5	2
Samples showing less than 15 free pus cells per average field.....	1	1
Samples showing less clumped pus and epithelial cells, 20 to 100....	14	0

The table of individual cow samples were from three different herds in which cow troubles had been traced from market milk examination. The samples of market milk were consecutive ones in the interim between market milk samples that showed trouble, that is, selected to the extent of not showing herd troubles.

We offer the accompanying tables to show how small may be the cell content of individual cows of one herd in which there was trouble, contrasted with one to show how much might be the trouble encountered in lax milk producers:

TABLE 2. CELL CONTENT OF MILK FROM HERD IN WHICH THERE WAS TROUBLE, CONTRASTED WITH THAT FROM HERD CARELESSLY HANDLED

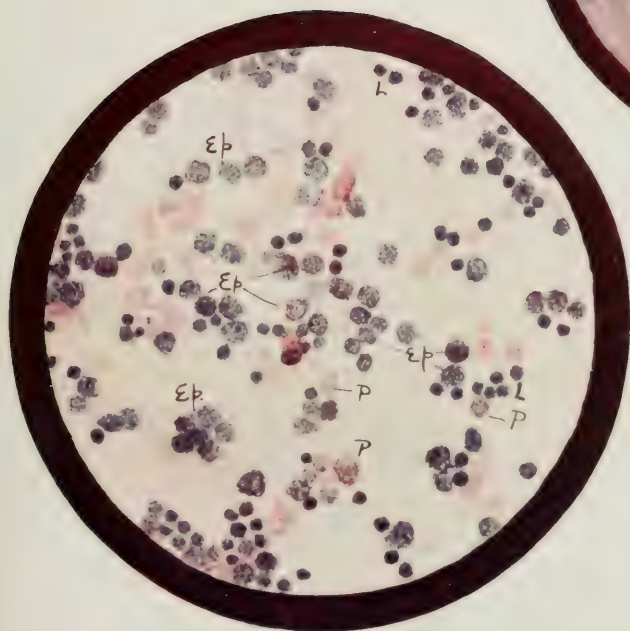
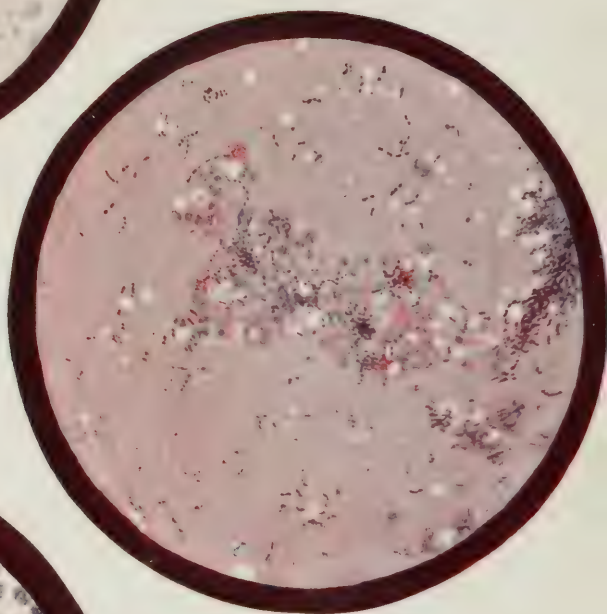
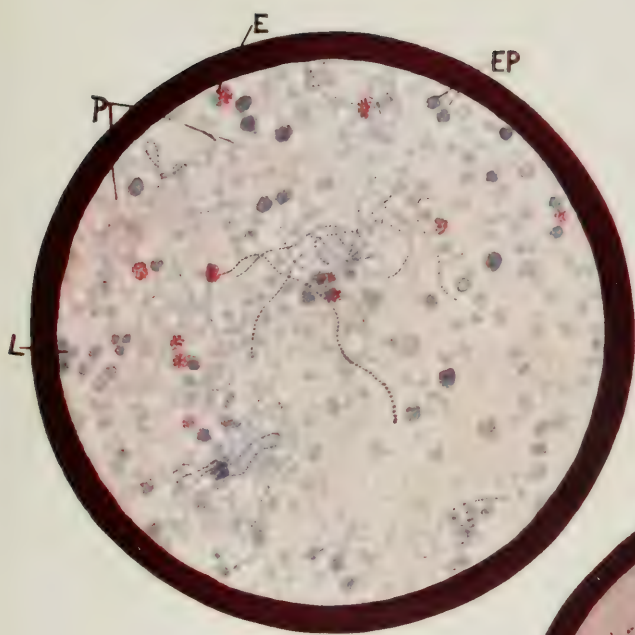
Cow No	Epithelial Cells		Polymorpho-nuclears		Eosinophils		Lymphocytes		Red Blood Cells	
	1 Herd	2 Herd	1 Herd	2 Herd	1 Herd	2 Herd	1 Herd	2 Herd	1 Herd	2 Herd
1	2	2	0	1	0	0	4	0	0	0
2	1	3	0	†*	0	15	2	0	0	0
3	0	5	0	50*	0	0	0	0	0	0
4	1	1	1	1	1	0	0	0	0	0
5	3	1	100*	2	3	0	0	0	4	0
6	15	0	†*	0	25	0	0	0	0	0
7	2	5	3	1	0	0	0	0	0	0
8	1	2	1	0	0	0	0	0	0	0
9	1	30	0	65*	0	2	0	0	0	0
10	0	25	0	30*	0	0	0	0	0	0
11	0	5	0	25*	0	0	0	0	0	0
12	2	3	0	10	0	0	0	0	0	0
13	0		0		0		0		0	
14	0		1		0		0		0	
15	1		0		0		0		0	
16	1		0		0		0		0	
17	1		1		0		0		0	
18	1		1		0		1		0	

\* Clumped. † Uncountable.

Out of the first herd of eighteen cows we have two cows at fault; one showed garget, the other an infected quarter. The second herd showed five cows at fault out of twelve, and all of them on examination showed varying grades of localized single-quarter, udder involvement. The producer of the milk of the second herd had picked out the cows previously, but because the milk was not "real stringy," and because he was short of milk, thought it would be safe enough to include these cows.

In the article under criticism, there is given a short report on the wide variation in the cell content on comparative counts of the fore-milk, the middle-milk and the strippings, examination of fifteen samples showing 53.85 per cent. increase of the strippings content over that of the fore-milk, and 52.14 per cent. in the strippings over the middle-milk. If this is put the other way, it reads that the fore- and middle-milk vary by but 1.74 per cent., while the strippings contain all the cells. This was of interest to us, in that we had not previously cared what portion of a cow's milk was sent to us for examination for inflammatory or minor grade troubles. Would this modify our results? Secondly, what might be the difference of cellular content in a differential count of normal, and, of more importance, of infected animals. Having gained an impression during the past four years' work on milk that there might be some relation between the cellular content of milk other than pus cells, and the period previous to, or following calving, together with the factor





#### EXPLANATION OF PLATES

Ep = Epithelial cells.

E = Eosinophils.

P = Polymorphonuclear neutrophils.

L = Lymphocytes.



of the age of the cow, we asked one of our most careful producers to pick us out six good cows of varying ages and varying terms following calving. We already appreciated that the majority of the minor cow troubles follow calving; would the strippings of cows at this time tell us anything that the first milk would not?

The data will be found in Table 3.

TABLE 3.—CELL CONTENT OF STRIPPINGS FROM SELECTED COWS AT VARIOUS PERIODS AFTER CALVING

Cow 1. Young cow, one month following calving:

Fore-milk.....	4 epithelial, 6 polymorphonuclears (free)
Middle-milk.....	2 epithelial, 4 polymorphonuclears (free)
Strippings.....	4 epithelial, 3 polymorphonuclears (free)

Cow 2. Young cow, three weeks after calving:

Fore-milk.....	3 epithelial, 1 polymorphonuclear, 1 lymphocyte
Middle-milk.....	5 epithelial, 1 polymorphonuclear, 1 lymphocyte
Strippings.....	20 epithelial, 6 polymorphonuclears (free)

Cow 3. Young cow, seven months after calving:

Fore-milk.....	2 epithelial, 4 polymorphonuclear (free)
Middle-milk.....	5 epithelial, 2 polymorphonuclear (free)
Stripping..s.....	10 epithelial, 8 polymorphonuclear (free)

Cow 4. Young cow, eight months after calving:

Fore-milk.....	1 epithelial, 0 polymorphonuclear
Middle-milk.....	3 epithelial, 1 polymorphonuclear
Strippings.....	4 epithelial, 1 polymorphonuclear

Cow 5. Ten years old, one year after calving:

Fore-milk.....	3 epithelial, 4 polymorphonuclear (free)
Middle-milk.....	4 epithelial, 4 polymorphonuclear (free)
Strippings.....	4 epithelial, 6 polymorphonuclear (free)

Cow 6. Ten years old, three weeks after calving:

Fore-milk.....	22 epithelial, 150 polymorphonuclear (clumped)
Middle-milk.....	60 epithelial, 20 polymorphonuclear (clumped)
Strippings.....	38 epithelial, 150 polymorphonuclear (clumped)
	2 eosinophils. 2 red blood cells.

The last cow was stated to have been out of condition and but for being in-calf would have previously been sold for beef. Typical long-chain streptococci were present in the three samples of the last cow.

Comparison of this data bears out the contention that the strippings may contain 50 per cent. more cells, as in two out of five uninvolved cows here given, but that in the single involved case, the fore-milk gave as much data as the strippings. It might be well, if there is any number of pus cells to be determined as a standard, that equal portions of fore-milk, middle-milk and strippings be obtained, yet for the purpose of diagnosis, this would not seem to be necessary.

We might well relate a recent personal experience of how exact this differential smear method is. We provide for a boy 2 years of age a milk produced by one of the most careful dairymen of this vicinity, who

rightly charges an extra price for his milk, and who is generally recommended as one producing one of the best milks for babies.

The boy refused this milk only at intervals the first day after a return from the country where he had been for a week. The following morning, having a diarrhea, we examined the milk and found but an average of 7 and 8 polymorphonuclears per field and an absence of streptococci. The pus cells were clumped, and incubation of the sample failed to show streptococci. A specimen the following morning showing the same findings, we believed it was either the beginning or ending of some cow trouble. That day we were asked from three different sources, each one a family where there was a baby, on this milk, ill with diarrhea for from four days to a week, if there was any trouble with this producer's milk. We asked the producer to have his herd gone through for some minor grade of cow trouble, giving him the above history. Unable to find anything wrong, his examination was followed by a veterinarian with no better results. In the meantime, we were told of two further cases of babies on that milk ill with diarrhea. We then volunteered to examine the individual cows through milk samples from each. In rubbing up the sediments of the 50 samples sent in, one was distinctly ropy, and on examination showed uncountable pus with accompanying chain-streptococci. Of the remainder, two showed average fields of 2 and 3 pus cells, two showed red blood-corpuscles, averaging 4 and 5 per field. The latter samples were from cows, one in for the first time, the other had been in for twenty-one days. Of the two samples showing the few pus cells, one was from a cow in heat, the other from a cow being dried off. The cow showing the main trouble was apparently free from disease, and is being watched for developments. We suspect that this cow is tuberculous and later shall ask for the proof if the trouble does not clear up.

A coincidence might be spoken of here. At the same time, with relative freedom from sore throats, a pediatrician told us of three cases of injected throats, high temperature and gland enlargement, though without the prostration of the usual streptococcus infections. These three cases were in different families, but on the same milk.

#### CONCLUSIONS

Clumped polymorphonuclear and eosinophilic leukocytes, in whatsoever numbers, accompanied by long-chain streptococci, mean cow troubles. Absence of streptococci does not mean that they will not be found when the original source of the trouble is located.

A differential blood-stain is a most important essential.

The Doane-Buckley volumetric method, scientifically accurate for cell counts, is inferior to a less accurate but differential count.



Laboratories setting any standard for a pus cell content as meaning cow troubles will frequently miss opportunities for preventing further infections.

NOTE.—Since this was written we have received the Report of the New York Milk Committee, and believe that this article answers the questioned findings of Articles 6, 7 and 8 of the Appendix. We would again emphasize the fact that it is not clumped cells (which may be clumped epithelial cells) which suggest inflammatory troubles, but clumped polymorphonuclear or eosinophilic cells. Again, we take issue with "chain-forming streptococci with at least six elements in a chain, alone, as sufficient to suggest udder troubles." That it is not, we have shown in a previous article. We are at present at work on a further article on streptococci in milk with further data on this point.

## THE FURTHER STUDY OF THE ANATOMY AND PHYSIOLOGY OF THE INFANT STOMACH BASED ON SERIAL ROENTGENOGRAMS \*

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Although the advances in roentgenology of the internal organs during the past few years have been truly remarkable, developing it into a highly specialized division of medical science, comparatively little research work has been done in the department of pediatrics. This was apparently not due to lack of inclination, but to the natural limitations imposed by a technic not sufficiently developed to make extended work with infants and young children possible.

The long exposures formerly necessary made it impractical to get radiographs of unruly infants with any detail, and, furthermore, there was always the danger of injury. Anesthesia was therefore often necessary when dealing with these young infants.

Flesh and Pietri in 1911 did pioneer work in this direction when they attempted to determine the normal stomach of nurslings and children, using bismuth or barium in their feedings. Their findings are mainly based on the results of fluoroscopic examination. Although this method is valuable as an accessory in such a study as ours, it had the great disadvantage of introducing the element of the personal equation, not allowing the findings to be checked up by other observers. As will be indicated below, their findings cannot be substantiated in the light of more modern methods.

The radiographic work was done in the Edward N. Gibbs X-Ray Laboratory (Carnegie Laboratory, New York University) by the director, Dr. L. T. LeWald.

### TECHNIC

All the radiographs were made with the subjects in the vertical position. All were taken with the plate at a uniform distance of 24 inches from the anode. The exposures were all instantaneous and taken at the height of inspiration. Markers were placed on the ensiform and umbilicus. The tube was focused on the umbilicus.

Bismuth subcarbonate was mainly used, with the exception that bismuthoxychlorid was employed when an absolutely neutral salt was required. The proportion of bismuth used was approximately 10 gm. of bismuth to the 100 c.c. of feeding. The majority were fed by gavage unless a special experiment relating to the food itself was in progress.

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\* Read at the meeting of the American Pediatric Society, Washington, D. C., May, 1913.

It was natural for the early observers to compare their findings with recognized types of adult stomachs which had become, so to speak, standard—such as the Holz knecht type or the Rieder or “J”-shape or fish-hook type, which is the accepted type of adult stomach. The child’s stomach approaches it more nearly after the second year. It was found, however, that the form of the stomach depended on the age of the child and the character of the food ingested, but on account of the imperfect apparatus they did not find that the x-ray gave them any help in studying the functioning ability of the stomach.

#### METHOD OF STUDY PURSUED

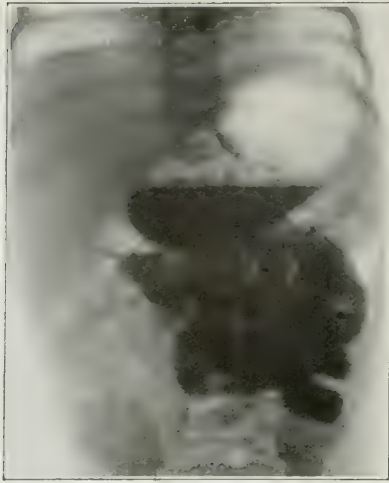
Our own study was planned for the purpose of determining if possible (1) the normal size and shape of the infant’s stomach; (2) its relation to the neighboring organs; (3) the influence of the internal organs on the viscus; (4) its behavior under differing amounts of food; (5) influence of different types of food as liquid or solid, acid or alkaline; (6) its peristaltic action; (7) the motility; (8) the passage of food through the gastro-intestinal canal; (9) the application of this knowledge to certain pathological conditions.

The age of the infants studied varied from the new-born of 2 days to 20 months. Serial Roentgenograms made this study possible. The reproductions eliminated the personal equation and enabled us to reach certain conclusions.

At first infants were purposely selected at random; later those considered quite normal were studied, and finally those showing pathological conditions, as malnutrition, rickets, syphilis, pyloric obstruction, spasmodic, tuberculosis, etc. The interval between the administration of the meal and the first exposure was from one to five minutes. Subsequent exposures were made at intervals of ten minutes to twenty-four hours in a given case, depending on the character of the experiment under way. We did not lose sight of the fact that this work was one-sided and that certain elements of error might occur, but we did hope that we could add something to the investigations previously made in physiological laboratories, eliminating the error of test-tube work and interfering as little as possible with the natural processes going on in the infant’s stomach.

At this point it may be of interest to state that independently of our efforts and unknown to us, Alwens and Husler of Frankfort were engaged in a problem apparently along similar lines; wherein our findings differ from these observers will be indicated later.

We approached this work with rather fixed ideas as to the natural conformation of the infant’s stomach, but these were soon dispelled. Our ideas were those generally accepted, and it may not be amiss to quote from some standard text-books the description of this viscus, as it will



Series A—Figure 1.



Series A—Figure 2.

Fig. 1.—Series A. Baby T., aged 2 days; nursling; 13 drachms fermented milk and bismuth introduced two hours and twenty-five minutes after last nursing. Exposure one minute after administration of food. Note size and shape of stomach and the gas area; a fairly large quantity of food has passed through in this time.

Fig. 2.—Series A. Same infant as in Fig. 1. Exposure after forty minutes. Note contraction of stomach and that large proportion of the food has entered the intestine.



Series B—Figure 3.



Series B—Figure 4

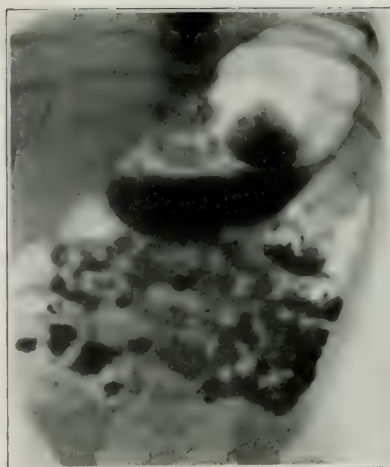
Fig. 3.—Series B. Aged 2 days; breast fed; 15 drachms given two hours and thirty minutes after last nursing. This exposure two minutes after the feeding. Note large size of this new-born stomach, about one-half gas and one-half food; a considerable amount of food has passed through pylorus in two minutes.

Fig. 4.—Series B. Same as Fig. 3. Thirty-seven minutes after feeding; pyloric end still to right side of median line; food throughout jejunum.





Series C—Figure 5.



Series C—Figure 6.

Fig. 5.—Series C. Baby B., male; aged 4 days; nursing baby. Exposure after two minutes;  $1\frac{3}{4}$  ounces food given two hours and forty minutes after last feeding. Note large size and peculiar shape of stomach; greater curvature at the umbilicus; food already extruded into jejunum.

Fig. 6.—Series C. Same infant as in Fig. 5, thirty minutes after feeding; the greater part of the food has passed through into the small intestine; stomach has contracted only slightly. Remarkable decrease in amount in twenty-eight minutes.



Series D—Figure 7.



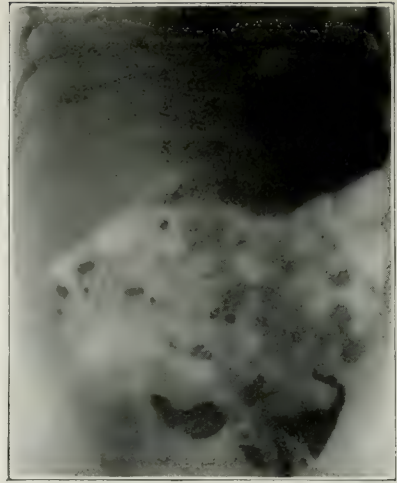
Series D—Figure 8.

Fig. 7.—Series D. Baby L., aged 4 days; nursing; 15 drachms bismuth mixture about three hours after last breast feeding. Exposure after two minutes. Note large gas area; pars pylorica is visible; some food already in jejunum.

Fig. 8.—Series D. Same infant as in Fig. 7, twenty-three minutes after feeding. Note the transformation in shape to tobacco-pouch form. Stomach almost empty after twenty-three minutes. Food throughout small intestine. Note stream of food pouring out through pylorus.



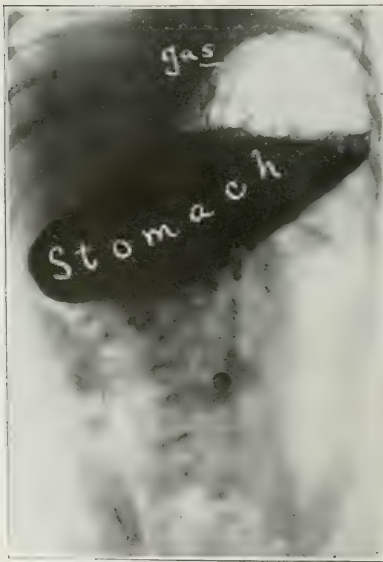
Series E—Figure 9.



Series E—Figure 10.

Fig. 9.—Series E. Baby P., aged 11 days; nursing; two hours and twenty minutes after nursing  $2\frac{1}{2}$  ounces bismuth-milk mixture introduced. Exposure after five minutes. Note amount of food for age and stomach only one-half filled; large gas area; considerable portion of viscus passes to right of median line; greater curvature here well marked and reaches the umbilicus; only traces of food have gone through.

Fig. 10.—Series E. Same as Fig. 9, forty-five minutes after feeding; a peristaltic wave is seen passing over the greater and lesser curvature; the antrum is drawn out spindle-shaped; large deposits of bismuth appear low down in intestine.



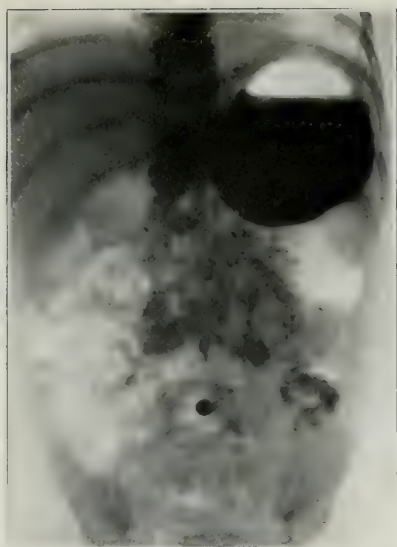
Series F—Figure 11.



Series F—Figure 12.

Fig. 11.—Series F. Baby aged 9 weeks; normal baby; breast fed; complementary feed just begun; 2 ounces bismuth mixture given. Exposure two minutes later. Scotch bag-pipe form; pylorus 4 cm. to right of median line; large amount of gas in cardiac end.

Fig. 12.—Series F. Same as Fig. 11. Twenty-four minutes after feeding; remarkable decrease in amount of food in this interval; food is seen in jejunum.



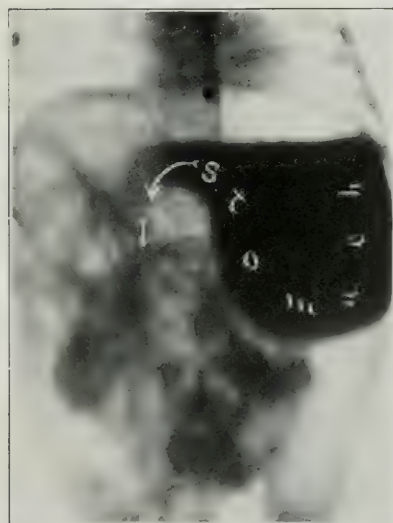
Series G—Figure 13.



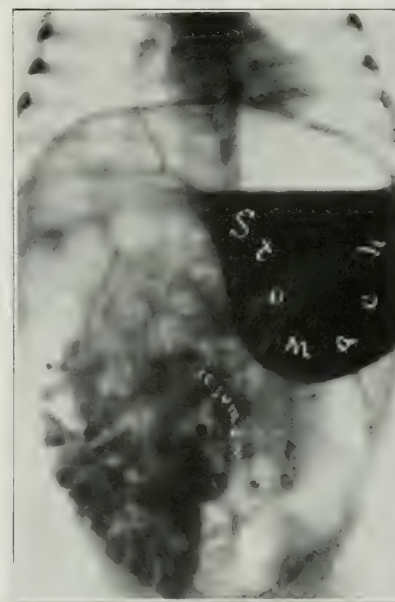
Series G—Figure 14.

Fig. 13.—Series G. Baby J. J., aged 2 months; weight 7 pounds; always artificially fed; poorly developed; 45 c.c. bismuth mixture introduced. Exposure after five minutes. Illustrates tobacco-pouch or retort form (a form more apt to occur in weaklings); note amount of food in small intestine; stomach entirely to left of median line; bismuth pouring out.

Fig. 14.—Series G. Same as Fig. 13 after forty minutes; shape has changed from retort form to pear shape; child nursed 22 drachms eagerly twenty minutes after gavage feeding; no admixture of the food has taken place; the gas area increased, probably through sucking action.



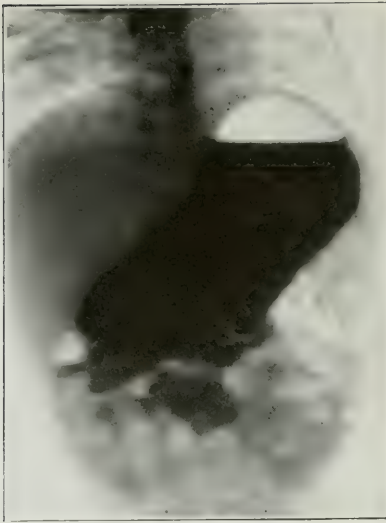
Series H—Figure 15.



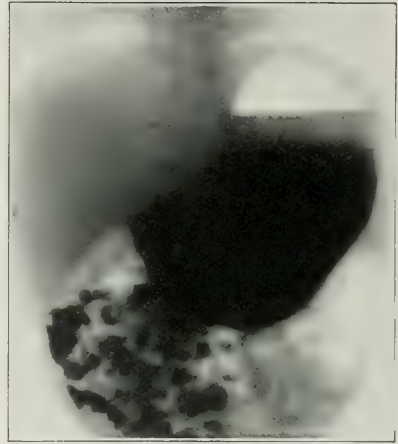
Series H—Figure 16.

Fig. 15. Series H. H. W., aged 4 months; artificially fed; malnutrition; 125 c.c. bismuth milk mixture; eight minutes later stomach pouch or retort form; pylorus in median line and relaxed; stream of food pouring out. Note amount of food that has escaped in this interval.

Fig. 16.—Series H. Same as Fig. 15 after fifteen minutes; large amount of gas in cardiac pole; the heart pushed upward thereby.



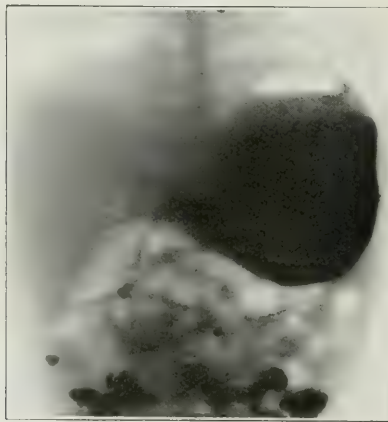
Series I—Figure 17.



Series I—Figure 18.

Fig. 17.—Series I. A. S., aged 5½ months; weight 9 pounds, 14 ounces. Diagnosis: Rickets with enlarged liver and spleen; pulmonary tuberculosis. Took 8 ounces bismuth milk mixture. Exposure five minutes later. Previously fed on a proprietary food; stomach much enlarged; extends well over to right of medium line; the shadow of the liver and tuberculous deposits in the lung are well shown.

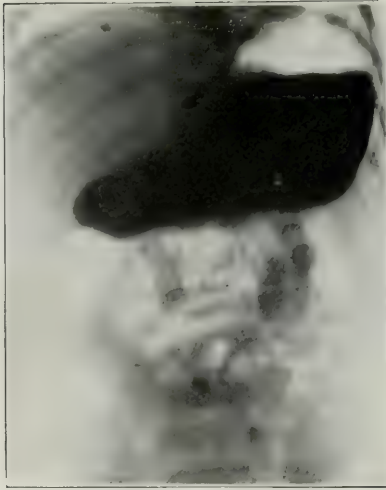
Fig. 18.—Series I. Same as Fig. 17 after twenty-five minutes; stomach contracting on its contents. Note change in shape; possibly the precursor of the water-trap type of stomach; extruding large quantity of food.



Series I—Figure 19.

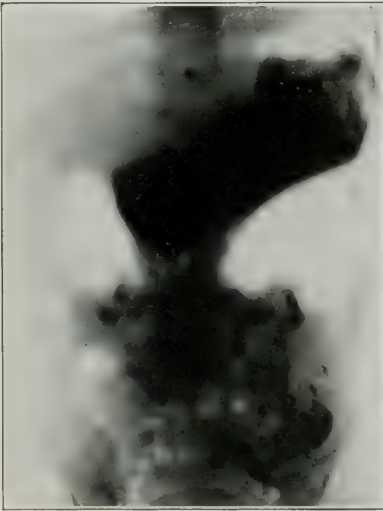
Fig. 19.—Series I. Same as Fig. 18 forty-five minutes later. Conformation entirely changed; only small amount of gas is left; food is seen passing out of pylorus in median line.



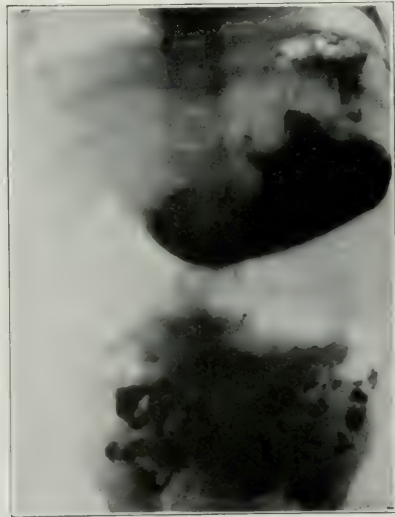


Series L.—Figure 20.

Fig. 20.—Series L. F. L., aged 7 weeks; weight 10 pounds; artificially fed practically from birth; 100 c.c. of bismuth-milk mixture. Exposure after five minutes. Note horizontal position and pyloric end under right lobe of liver.



Series L.—Figure 21.



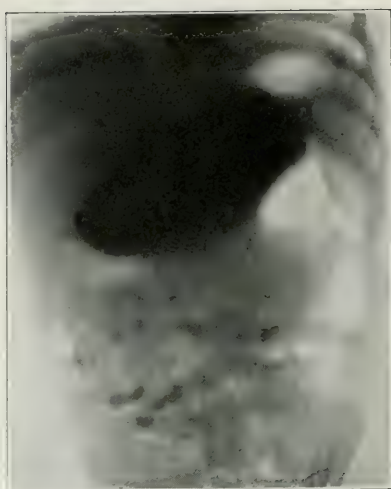
Series L.—Figure 22.

Fig. 22.—Series L. Same as Fig. 20. Forty-five minutes after initial feeding the foods have not intermixed.

Fig. 21.—Series L. Same as Fig. 20 after twenty minutes; marked diminution in size; food being forced into intestine; baby now given 3 ounces of its usual formula twenty-five minutes after the feeding by gavage. Note subsequent exposure.



Series N—Figure 23.



Series N—Figure 24.

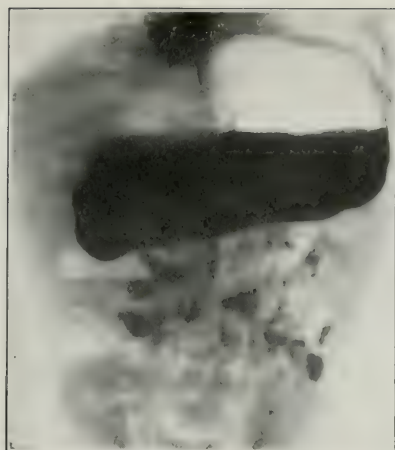
Fig. 23.—Series N. E. P., aged 3 months; weight 10 pounds, 4 ounces; 100 c.c. top milk, (20 per cent.) + 2 drachms lime-water and bismuth oxychlorid (neutral) used. Example of delayed pyloric opening; one minute after feeding practically no food has passed.

Fig. 24.—Series N. Same as Fig. 23 after twenty minutes; in comparison with other feedings an exceedingly small amount of food has passed through.

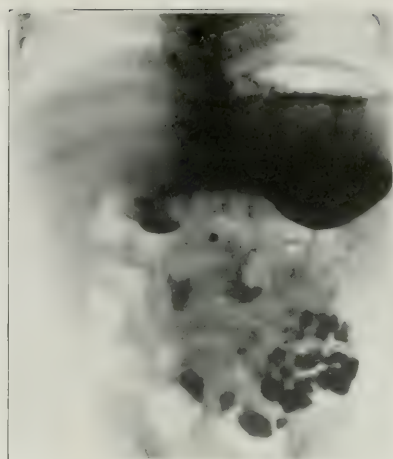


Series O—Figure 25.

Fig. 25. Series O. G. M., aged 4 months. Diagnosis: Rickets; spasmophilic infant. Feeding: 6 ounces of 20 per cent. cream,  $\frac{1}{2}$  drachm of sodium bicarbonate with 10 per cent. bismuth. Exposure after five minutes. Note horizontal position and large gas area with enormous dilatation of cardiac pole; little food has passed.



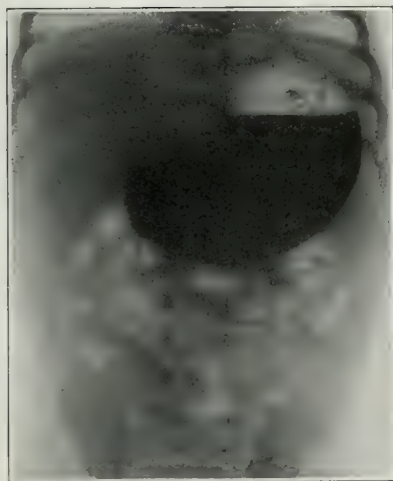
Series O Figure 26.



Series O—Figure 27.

Fig. 26.—Series O. Same as Fig. 25 after fifteen minutes. Amount passed through in this interval decidedly small by comparison.

Fig. 27.—Series O. Same as Fig. 25 after one hour. Change of form accompanied by the exit of some food after an interval of forty-five minutes. Since last exposure, alkalinity apparently has been overcome.



Series P Figure 28.



Series P—Figure 29.

Fig. 28.—Series P. McC., nursing baby, 2 days old, well nourished; birth-weight  $7\frac{1}{2}$  pounds. Exposure made two minutes after having food, consisting of 6 gm. bismuth in 60 c.c. of milk. This is considered to be one of the normal types of infant stomach.

Fig. 29.—Series P. Same as Fig. 28 twenty-eight minutes after original food. Note the amount of food which has passed through the pylorus and how it is scattered through the small intestine. This is considered a normal rate of emptying.

emphasize the importance of checking up the present-day anatomical knowledge with Roentgenograms.

#### ANATOMY

Cotton, in his text-book on "Diseases in Infancy and Childhood," says of the stomach:

Contrary to generally accepted statements the general form and position of the stomach are very similar to the empty and collapsed stomach of the adult, but in consequence of the large size of the left lobe of the liver, the whole anterior surface is usually covered by that organ. When the stomach is filled, the movement of its pylorus towards the right side is probably impeded by the large liver, thus tending to make the axis more vertical. The fundus is usually less pronounced and the valvular constriction of the cardiac orifice is wanting, allowing easy regurgitation of the contents. The average capacity at birth is less than an ounce.

In Holt's *Diseases of Infancy and Childhood*, the description reads thus:

In the newly-born child it lies somewhat obliquely in the abdomen, and at the end of infancy has almost reached the transverse position. The stomach at birth is nearly cylindrical, but the fundus increases in size rapidly during the first year, although it does not reach its full development until quite late in childhood.

Chapin and Pisek in their book say:

The stomach is somewhat like a vertical sac at birth, but gradually develops in a horizontal direction.

As a result of our investigations we are forced to the conclusion that there is no definite normal type of stomach in the infant. It is horizontal rather than vertical in position when compared with the adult type, and follows certain rather definite forms. We can distinguish (1) the ovoid, or Scotch bagpipe shape of Fleisch and Pietri; (2) the tobacco pouch (or retort shape of Alwens and Husler), as previously described by us; (3) the pear-shaped stomach with base above and to the left. The shape of the stomach does not even depend directly on the amount or character of the food ingested, but rather on the quantity of gas which it contains or acquires. Furthermore, its limits are greater than we were accustomed to believe, extending to the liver on the right and at times filling the entire transverse space from one abdominal wall to the other.

The upper border or smaller curvature may or may not be seen in the Roentgenograms, while the lower border is formed of an indeterminate portion of the viscus.

Of particular interest from the standpoint of diagnosis is the position of the pylorus. In the majority of cases this is found comparatively high and behind the pyloric third; at times its position cannot be determined even though we clearly see that the food and bismuth has passed



out of the viscus. This is especially true in the tobacco pouch form, in which the pylorus is forced posteriorly.

Alwens and Husler report that they have observed a change in form from the tobacco pouch to the bagpipe variety after the intestines have been emptied. This finding also occurred in our series (Figs. 13 and 14). The Rieder type was observed only once, occurring in a six-months old infant (Fig. 18). It appeared first as the bagpipe form, changed to a Rieder and then to a retort form. When semi-solid food is being taken comparatively little gas is swallowed and the stomach is more apt to simulate the adult or Rieder type. The question of contained gas, or introduced gas, is an interesting one. In some cases the gas seems to act as a buffer, preventing the over-distention of the stomach with food. As a rule, the broader or more protuberant the abdomen of the infant, the greater the amount of gas the stomach contains.

#### PYLORIC ACTION

One of our most noteworthy observations related to the rapid passage of food out of the pylorus—in a number of cases bismuth was seen in the duodenum one minute after the food had been introduced into the stomach by gavage, the average time being five minutes; in one case of the tobacco pouch, or retort form, the action was not unlike that of a siphon (Fig. 15); after the greater part had passed through the pylorus the emptying action became slower. Except in the instances in which semi-solid food (farina and bismuth) or cream were fed, the viscus tended to empty itself with unsuspected remarkable rapidity. How this action can be taken advantage of in cases of pyloric stenosis and pylorospasm has been indicated in a previous article.<sup>1</sup>

We must also question in this connection the advice of those who, like Grulee, recommend placing all infants on four-hour feeding intervals, since a large number of stomachs practically empty themselves within an hour. In abnormal cases, as in infants having chronic disturbances of nutrition the stomach began to empty itself very rapidly, and the emptying time was even shorter. If further proof is necessary as to the rapid emptying of the infant's stomach, it can be found in the fact that infants, to whom it was offered, greedily took their bottles of modified milk thirty to forty-five minutes after the feeding by gavage. This is well illustrated in Series G (Figs. 13 and 14), and also in Series L (Figs. 20, 21 and 22), Roentgenograms of an infant of 7 weeks who took 3 ounces of bottle feeding forty-five minutes after the administration of 3½ ounces of fermented milk and bismuth.

We attempted also to corroborate the suggestive experiments of Cowie and Lyon on the pyloric opening and closing reflex. It was impossible

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1. Arch. of Pediat., December, 1912.

to record or obtain Roentgenograms of the action of the pylorus itself which they so well described, because as has been said above, the pylorus and the first part of the duodenum are rarely visible, but the retarding action, for example, of alkalies, which they record, is well shown in Series N (Figs. 23 and 24). Here the stomach did not empty itself for four and one-half hours. Again giving an infant, for example, one type of food, as fermented milk with bismuth, and then allowing it to take its bottle containing modified milk, we were able to verify the work of Cannon and the observations of Grutzer and Sick, who found that foods in the stomach do not tend to intermix. Sick goes even further and says that with fluid food we have the formation of true layers, so that in milk digestion we have the whey expelled first, later the casein and last the fat content.

#### STOMACH TONE

Observations on the contracting power or tone of the stomach can also be made by this method. The normal stomach tends to expel its gas accumulation soon after the entry of food; it tends to envelop or surround the food, to diminish in size generally, to shorten its axis by drawing upward and to the left partly under the shelter of the diaphragm. This action is not as marked in infants who retain the tobacco-pouch form; here we observe merely a diminution in the size of the viscus.

A peristaltic wave passing along the greater curvature is caught on the plate at times (Series N; Fig. 23). It is more apt to be seen in cases of habitual vomiting or in infants having pyloric stenosis or spasm. We have very seldom observed the wave along the lesser curvature, but this is not remarkable in view of the fact expressed above that the smaller curvature is seldom in sight.

In conclusion it may be said that the field of research in this direction has merely been opened. There are many observations, particularly dealing with the food in the intestines, which need close study, especially in their relation to disturbances of the bowel function so frequent in early life.

How much help we can obtain in our pediatric practice by a Roentgen examination of the alimentary canal in infants and children will be apparent by a study of the statements just made and the illustrations shown.

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## URINARY LITHIASIS IN INFANCY \*

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At first thought, urinary stone and especially stone in the kidney is a subject pertaining to adult life. The discovery of the condition, especially of renal stone, in an infant or small child provokes an additional interest and concern owing as well to the tender age of the patient as to its comparative rarity of discovery before death.

Our chief sources of light on this subject are to be sought in the recent reviews, more especially of the German and French. In earlier literature the treatment of the subject has been with reference to older children, including those up to 15 years of age. In some of our modern textbooks, no mention is made of renal stone in infants; in some others, the subject is given scant attention. Stone in the bladder and gravel in the urine occupy places in the literature extending many years back, the treatment by medicinal and dietary measures being placed in the foreground. Until recent years—notably since the advent of the x-ray—little attention was given to the surgical aspect of stone in the infant kidney or ureter, though bladder stones have for generations been treated surgically.

My attention was first attracted to this subject a few years ago as the result of a case in an infant of 16 months which came under my observation. The interest attendant on a study of the literature led me to collect considerable material and in this manner the present paper found its beginnings. As a basis for discussion, the history of the above-mentioned case here follows:

### CASE REPORT

*History.*—The infant was a 16-months'-old male, born in Minnesota, of Bohemian parents, neither of whom ever complained of any urinary trouble. The mother's brother, a lad of about 7 years, had been known to pass gravel with the urine in his early days.

The baby had been circumcised at 4 weeks of age, was breast-fed for the first year and suffered none of the usual children's diseases, with the possible exception of "colics," until the onset of the present trouble. Until several months of age, according to a certain custom, the baby was kept wrapped about, arms confined to the sides, by a long scarf or long quilted band allowing of no exercise of the arms or legs, except once daily when the band was removed for a short time.

*Examination.*—I saw the infant late one December afternoon, 1909. He had not urinated for twenty-four hours. Examination revealed a spherical stone

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\* Read in the Section on Diseases of Children of the American Medical Association at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.

(Fig. 1 "X") impacted in the extreme end of the urethra. On the extraction of the obstructing stone the baby passed a large teacup-and-a-half of urine. The stone, weighed later, proved to be  $\frac{3}{4}$  grain and by analysis was composed of earthy phosphates. Three months following this onset of trouble the father brought to me several smaller stones which the infant had passed. Radiographic examination was advised to determine if possible the presence of other stones in the urinary tract. After a delay of three months the parents brought the patient for such an examination. The result of such examination, six months after the onset, shows (Fig. 2) two stones in the right kidney, one in the bladder, and a third somewhat irregular shadow appearing at about the crest of the right ilium—probably ureteral stone. Radiographs a few days later substantiated the findings at the first sitting. Surgical interference was positively refused by the parents.

Plates taken about nine months after the first radiographs revealed the calculi as before (Fig. 3) but with some destruction of kidney substance. In addition, shadows in the region of the left kidney appeared, showing the formation of calculi in that organ. The infant continued to pass small calculi at intervals. About a year later the child was operated on in Chicago for bladder stone.

At the present writing I am in receipt of a personal communication from the father to the effect that the child is in fair health—at the age of  $4\frac{1}{2}$  years—though no relief has been attempted for the kidney stones. The same letter



Fig. 1.—Showing spherical stone "x," which was removed from child's urethra. The other stones were passed by the child at varying intervals.

also conveys the information that the child's uncle (the mother's younger brother, above referred to in the history) is just recovering from an operation for bladder stone "the size of a pigeon's egg." He was 10 when operated on, and my letter states that he had passed fine gravel which was first noticed when he was 3 months old and has done so at intervals since that time. During the last two years his condition has been very much worse.

The family history of stone in this case is of interest. As an example of extensive family occurrence it is interesting to note the experience of Clubbe, who operated on the three sons of a fisherman of Lowestoft, England, for stone, at ages of 2, 3 and 8. The father and mother always had gravel in the urine. The grandfather passed one and the grandmother passed seven stones. A great uncle was operated on for stone. Six uncles and four aunts all suffered from spells of gravel, and finally a cousin, an uncle's child, was accustomed to pass gravel.

Too much stress should not be laid on the family tendency, however. The experience of Clubbe is rather to be regarded as rare than common.



In Bokay's experience he has seen only one case in which he could lay any stress on heredity in the sense of families of stone formation.

Other cases of urinary stone are quoted by various authors as having

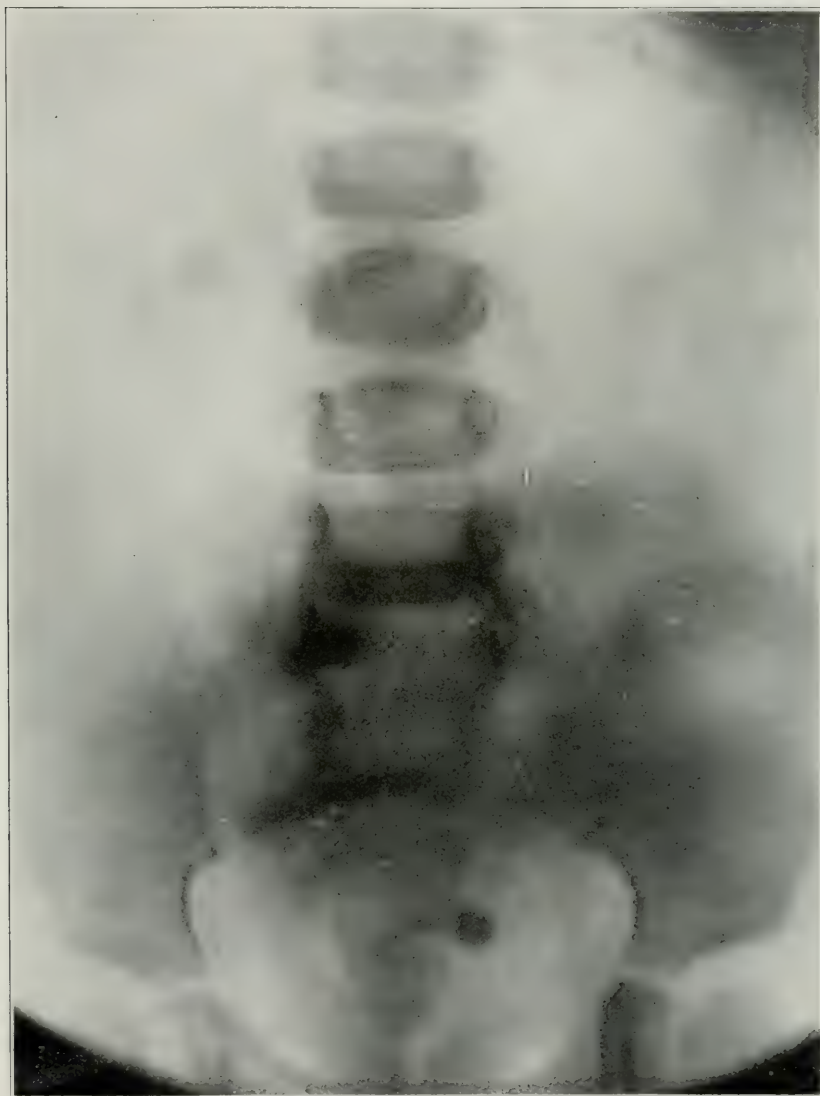


Fig. 2.—Radiograph showing two calculi in right kidney, one in the bladder and a third shadow at the crest of the right ilium—probably stone in the ureter.

been found early in infancy or even before term. Langenbeck found a calculus in the bladder of a six-months fetus. Southworth, in 1895, presented the New York Pathological Society with the kidney of a new-

born child containing calculi. Brendel quotes three cases two days after birth. Meigs records the recovery of a calculus post-mortem from the kidney of an infant of 6 months. Two cases of renal stone discovered in infants of 20 months are recorded by Hance and Partridge. The latter's case presented no symptoms of calculus during life. It was discovered at

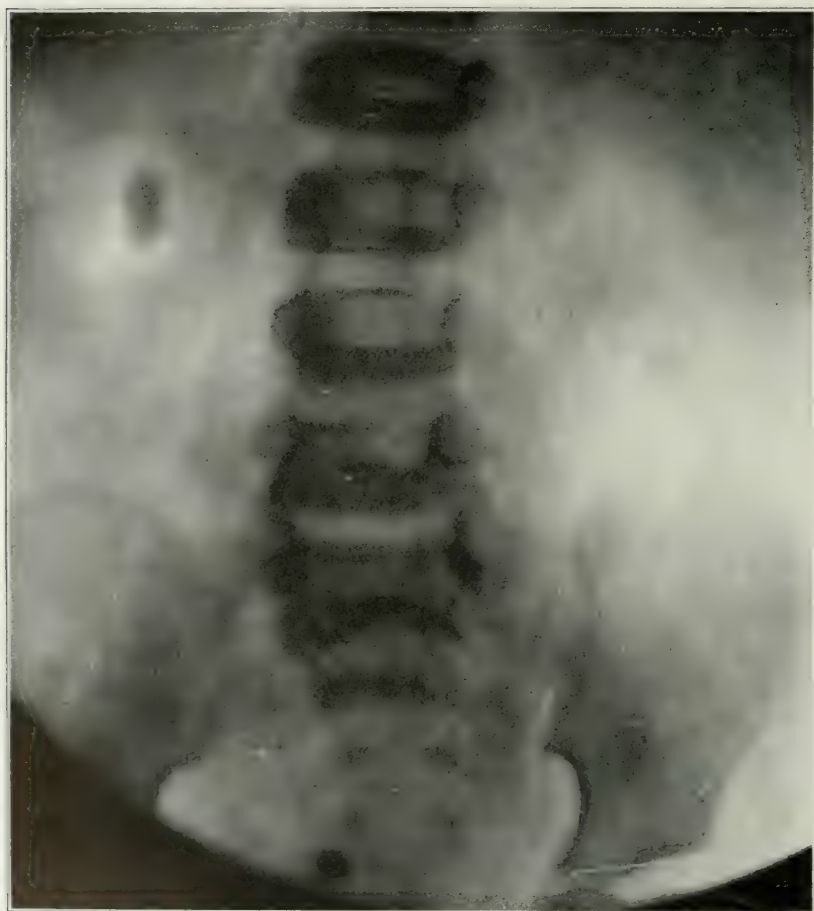


Fig. 3.—Radiograph, taken nine months after that shown in Fig. 2, showing two calculi in right kidney and destruction of kidney substance. Also the bladder stone as in Fig. 2. In addition, two shadows are shown in the left kidney region.

autopsy. Jacobson cites a case of a child operated on in which the bladder was found to be in a condition of complete incrustation. At autopsy both kidneys were found to be absolutely filled with stone. G. Newton Pitt records three cases of renal stone in infants, discovered at autopsy. The first was in an infant of 15 months. Death occurred

from diphtheria. A stone weighing 4 grains was found at autopsy. The second was 11 months old when death occurred from diphtheria. The kidney stone in this case weighed 2 grains. The third infant was 21 months old when death occurred from bronchopneumonia. Hematuria had been noticed during life in this case. The stone recovered at autopsy weighed also about 2 grains.

#### OCCURRENCE

Civiale found that 45 per cent. of 5,900 cases of calculus occurred in children, and that children under 5 years are especially prone to the condition. The principle of "survival of the fittest" holds its sway with remarkable tenacity respecting urinary stone. A high percentage of the known cases appear to be those discovered at autopsy. It will be seen by referring to Tables 1 and 2 that of the patients under 5 years, about 92 per cent. are 2 years or under, and that practically all of these are cases which have reached the autopsy table. In the past, therefore, it would seem that urinary lithiasis, especially of the renal type, laid just claim to a high mortality.

Holt, basing his information on 1,000 autopsies, says that small renal calculi are very common in infants, but that they are probably voided during the first two years of life because of the fluid diet of the first two years.

While it is possible that the fluid diet may influence favorably some cases, it is also possible that the fluid diet may in some cases be largely responsible for the condition of urinary lithiasis. As an instance let me quote Robin's goat-milk case: An infant of 16 months was raised on goat's milk. The infant passed uric acid gravel. Analysis of the milk showed excess of casein. Excess of azote or nitrogenous food was found to be the prevailing diet of the goat. The food of the goat was thereon changed, and very promptly the infant's nephritic colics disappeared.

Charvin and several others are inclined to the belief that renal stone in infants and children is a rare condition. Rafin, who collected 39 cases in infants and children either operated on or revealed at autopsy, says: "The small number of cases attests to the rarity of the surgical form of renal and ureteral calculus during infancy," and he then raises the question as to whether this is a real rarity.

Durand-Fardel and Civiale believe nephritic colic in the infant is not a rarity. Gibbons reports six cases in infants of 9 to 23 months. Bokay has collected in Hungary some 1,836 cases of urinary stone in infants and children of ages ranging as high as 15. Of these, 45 were 12 months of age or under, as follows:

Age Months	Cases
2½ .....	1
3 .....	1
5 .....	3
6 .....	6
8 .....	4
9 .....	4
12 .....	26

The bladder stone cases numbered 1,319; one-half the cases were urethral and nine of the cases were of kidney stones. The greater number of cases occurred at 3 to 4 years.

The literature is far from being replete with cases of renal stone discovered and treated, whether successfully or unsuccessfully, during life.

How important in the mortality statistics from birth to 2 or possibly 5 years is the factor of the stone or stones *per se*? How many of the bladder or kidney stones forcing themselves into recognition in later life might be discovered in infancy or childhood? These questions will be taken up later in the course of this paper.

According to Senator it is impossible to make a hard and fast morphological distinction between renal and vesical calculi. Carl Beck believes most vesicle stones come from the kidney. Porter says nephritic calculi are not relatively so rare very early in life as are vesicle calculi.

Certain it is that many of the calculi do not produce any morbid phenomena until they reach the bladder. Moreover, there are numerous instances on record to show that definite and very troublesome cases of stone discovered in young adult life had their origin during infancy or childhood. I have called attention above to the relative of my little patient who was operated on about nine years after gravel was first noticed in his urine. The cases quoted by Monsseaux and Charvin which are arranged in Table 3 are illustrative of this fact also.

The endemic, hereditary, dietary and systemic phases in the occurrence of urinary stone are ably reviewed by Hugh Young in Osler's *Modern Medicine* and will not be dwelt on here. It is a significant fact, however, that the children of the poor are more prone to harbor urinary stone than those of the rich. Von Preindlsberger, in reviewing his 271 cases about Bosnien-Herzegovina, claims that lithiasis is far more prevalent in the Christian population than in the Jewish, most likely by reason of the unfavorable conditions essential to living and the bad prevailing diet of the Christian children.

It is an established fact that males are subject to lithiasis far more often than are females. In the statistics given in Table 1 the males outnumber the females 2 to 1. Bokay's statistics show that only 4 per cent. were girls. Coulson's comparison places the figure at 5 per cent.



Rafin finds urinary stone occurs most frequently on the right side. While we have here in America no regions where lithiasis is essentially endemic, as in Egypt or in Asia, still the condition is known to be fairly evenly distributed over the different parts of this country.

TABLE 1.—SHOWING RECORDED CASES, THE RELATIVE AGES AND SEX PROPORTION AND THE PROPORTION OF AUTOPSY CASES\*

Name	Total Cases	Cases at Autopsy	Under 1 Year	1 to 5 Years	Male	Female	Not Stated
Rafin .....	39	28	0	5	24	11	4
Pitt .....	3	3	3	...	...	...	3
Charvin .....	45	10	0	...	...	...	?
Jacobson .....	1	1	0	...	...	...	1
Hance .....	1	1	1	...	...	...	1
Partridge .....	1	1	1	...	...	1	...
Meigs .....	1	1	1	...	...	...	1
Langenbeck..	1	1	1	...	...	...	1
Brendel .....	3	3	3	...	...	...	3
Clubbe .....	2	0	0	2	2	...	...
Southworth..	1	1	1	...	...	...	1
Aleksinski...	1	0	0	...	1	...	...
Jopson .....	2	1	0	2	2	...	...
Smythe .....	4	0	0	4	...	...	4
Sumpter .....	1	0	0	1	1	...	...
Porter .....	1	0	0	1	...	1	...
Monsseaux...	77	?	0	9	51	26	...
Comby .....	48	48	46	2	31	17	...
Joseph .....	40	40	38	2	27	13	...
Bokay .....	45	?	45	...	...	...	45
Mandble .....	1	?	0	1	1	...	...
Dun .....	1	?	0	...	...	...	1
Jaffrey .....	1	?	0	...	...	1	...
Drew .....	1	?	0	1	...	...	1
Nash .....	1	?	0	1	...	...	1
Totals ...	322	139	140	26	140	70	67

\* The males outnumber the females 2 to 1. Of the total number of 322 cases, 139, or over 43 per cent., are post-mortem cases.

#### ETIOLOGY

The etiology of urinary stone has furnished a subject for much discussion in past times. Heretofore divers theories have been advanced to explain the existence of such calculi. A traditional view holds that the mode of life, diet, and especially nitrogenous diet with wine, beer and little exercise, is conducive to stone. Again, any interference with urinary discharge is regarded as a predisposing factor. English believes a congenital narrowness of the urethra in the second year is a factor in vesicle

calculus in boys. Langstein states that in addition to uric acid infarction, endemic conditions have a decided influence on the formation of a calculus; also, that heredity, especially from gouty parents, and still further, the amount of calcium in the drinking water, are important factors. Phosphatic medication was supposed to have an influence in the occurrence of a stone in an infant case reported by Anozan. Comby states that the cause of stone formation is poor alimentation and inanition.

TABLE 2.—TO SHOW THE AGE DISTRIBUTION OF CASES OF RENAL CALCULUS IN INFANTS AND CHILDREN FIVE YEARS AND UNDER IN ONE HUNDRED SEVEN CASES\*

Name	Under 3 Mos.	3 to 6 Months	6 to 12 Months	12 to 24 Months	2 to 3 Years	3 to 4 Years	4 to 5 Years
Comby .....	11	17	18	2	....	....	....
Pitt .....	0	0	1	2	....	....	....
Monseaux...	0	0	1	2	3	2	1
Mandble ....	0	0	0	0	0	1	....
Joseph .....	12	15	11	2	....	....	....
Drew .....	0	0	0	0	0	0	1
Nash .....	0	0	0	0	0	0	1
Southworth..	1	....	....	....	....	....	....
Meigs .....	0	0	1	....	....	....	....
Partridge ...	0	0	0	1	....	....	....
Hance .....	0	0	0	1	....	....	....
Totals ....	24	32	32	10	3	3	3

\* From the above table it will be seen that ninety-eight cases or 91.5 per cent. of the total, are 2 years or under. It will also be found by comparing with Table 1 that practically all of the 91.5 per cent. are post-mortem cases.

The influence of the infectious diseases on urinary lithiasis cannot be ignored. M. Nove-Josserand is quoted by Rafin as having recorded a case of renal stone discovered by the radiograph and recovered at operation in a child who first had a mouth infection followed by bronchopneumonia and later by a grave osteomyelitis. The renal symptoms appeared at the close of the above series of complaints. He quotes, also, Eynard's case, in which the stone was perhaps the result of a grave impetigo. The association of various infectious diseases with urinary stone is also pointed out in connection with Joseph's cases, as seen in Table 4.

Albarran's classification of renal stones into *primary* and *secondary* stone has been widely used, and is utilized by Charvin in his study of forty-five cases in infants and children. The first form (primary) is considered to be due to or at least associated with gastro-intestinal dis-

orders, deficient alimentation or poor elimination. The second form (secondary) is considered to be due to bacterial activity, chemical modification of urinary constituents and precipitation of urinary salts. The primary is believed to occur in the very young and the secondary in older children, or to put it in another way, the secondary form does not occur in the very young infant.

On this problem of the origin of primary renal calculi, Schade furnishes an explanation based on certain scientific facts. To quote Robert Milne's summary of Schade's work:

We must comprehend what he means by the terms "colloids," "reversible" and "adsorption," as applied to this problem. "Colloids" are substances which appear to dissolve in water (e. g., mucin or fibrinogen), but are probably in a condition of suspension, since the osmotic pressure is not affected by their presence. A "reversible" substance is one which can be redissolved after being deposited from solution, for example, a crystal of magnesium sulphate. Mucin is a reversible colloid. Fibrin is an irreversible colloid. Adsorption is the property colloids have of holding in a solution inorganic substances to an extent greater than could be dissolved in an equal quantity of water. He would suggest that, for example, uric acid in urine is held there in its excess by adsorption, on urochrome and other reversible colloids.

Should the uric acid be in excess of the amount which the colloid can hold by adsorption, we can picture the uric acid being deposited on the colloid. Should the colloid be a reversible one, both colloid and deposit can be removed by more water. If the colloid be irreversible, e. g., if that uric acid be deposited on the surface of fibrin, then no amount of water will redissolve that irreversible colloid—the patient is forming a primary renal calculus which no mineral water or drug ever cured. The colloid is the source of the small amount of organic matter found in every primary aseptic calculus. The tendency of fibrin to form laminae is the reason of the laminations of these primary renal calculi, and lastly, to cure that patient we have only to diet him in the future to prevent excess of the substances which formed the stone; we have not only to tell him to prevent relative excess by drinking abundance of water, but we have to discover the cause of fibrinuria, or fibrin in the urine, which occurs apart from hemorrhage. This problem has still to be solved.

Joseph describes, in connection with his study of forty autopsy cases, a peculiar albuminous substance which he found beneath the kidney capsule and also in the Bowman's capsule, morphologically glairy and homogeneous, sometimes occurring in lumps and appearing like fibrin, much the same as the hyaline casts in the urine. He concludes that calculi are caused by renal changes. He observed in kidneys containing stones, changes which were the same as those in the opposite kidneys without stones.

It would be difficult to believe that infection plays any considerable part in the origin of stone during uterine life or in the very young infant. Morris states that the nucleus of calculi formed in infancy is generally urate of ammonium.

#### SYMPTOMATOLOGY

To await classical symptoms of calculus as may be encountered in the adult is to waste valuable time. Calculus may exist in the kidney without

giving rise to symptoms of any kind. Beck found that whenever there was a calculus in the bladder he found a renal calculus also. There may be serious paroxysms of pain which are the result of the incarceration of stone. Hematuria is not always to be expected, however, when stone is present. Pitt reports a case of stone found at autopsy in an infant of 15 months, in which case no blood had ever appeared on the napkin. The possibility of microscopic blood is to be considered here. The history merely states that the infant passed more water than the other babies in the family.

In the observation of Monsseaux, who reports some seventy-seven cases, hematuria was a sign in but eight of the cases. He mentions a hereditary disposition in forty-four of the cases. According to Durand and Civiale, nephritic colic is not a rarity. Small children are not, however, capable of indicating the site or the character of the pain. The older the child the less difficulty will usually be found. From the sudden onset of pain the child is apt to cry continuously, and while the pain may at first be in the region of one kidney or the other, later in the attack the pain is usually diffused over the abdomen. Nausea and vomiting may occur with greater or less frequency and present a bilious character. The absence of diarrhea will, however, be noted to remove suspicion from a possible essential gastro-intestinal disorder. The face is pale, and, in the words of Monsseaux, "the expression vividly reflects the pain in the suffering infant." After a few hours the crying and restlessness may cease and more or less small gravel may be found in the urine. Or the picture may be that presented by my case in which the first alarm was sounded by a suppression of urine due to an impacted urethral stone, the finding of which led to the suspicion of other stones in the urinary tract. Blood may be found only on microscopic examination. The tendency to a remission of the symptoms renders the condition very chronic in its course.

Mention is made of an occasional case in which urinary stone is associated with disturbances of the nervous system. Monsseaux cites one case in which injury to the head at the age of 6 months was followed by gravel in the urine. Aleksinski's case, having "nervous fits" at 2 years, which will be quoted further on, has also a suggestion of this nature in it.

#### DIAGNOSIS

An analysis of the urine cannot always be relied on to give specific information leading to the diagnosis of urinary stone, though the urine findings are often suggestive. Microscopic examination of the sediment in a suspected case may disclose blood or pus cells, or crystals of oxalate, phosphate or of uric acid. The urinalysis may, however, present certain constant characters in that the urine may be somewhat abundant, the



specific gravity 1.023, 1.025 or 1.030, the acidity often considerable and a fine precipitate of flakes of uric acid crystals, brilliant and orange colored, to be found, the uric acid being greater than normal.

The history of elimination of sand is an important matter to determine, if possible; also, the history of frequent or painful micturition should be recognized as suspicious of stone. Hematuria accompanies nephritic colic, especially with oxalic gravel, less frequently in the interval between crises of colic. Hematuria of bladder origin is thought by Monsseaux to be very rare in the infant.

Palpation of the kidney, ureter and bladder regions may not reveal the site of trouble until late in the attack. It should therefore be tried again. Eliot reports a case in which the kidney was very much hypertrophied, but was misplaced by an accumulation of gravel (presumably in the kidney-pelvis). Murphy's "first-percussion," in a modified form, may be used over the kidney regions at the back, by employing, instead of the fist as a pleximeter, fairly vigorous percussion with one or two fingers of the right (or striking) hand. This method may serve to differentiate between involvement of the right or left kidney early in the attack.

Differentiation must at times be made from affections of the liver (rare in the infant); also lumbago (rare), Pott's disease and appendicitis. In a case of Weill's, the latter was clearly to be considered in the diagnosis. Nephritis is not rare in the infant. Casts should be searched for. Renal tuberculosis in the infant generally runs an acute course. Other organs are involved. Cancer in infants or young children is not accompanied by renal or ureteral pain. Renal tumefaction should be sought and an examination made for symptomatic varicocele, "always pathognomonic to that age," according to Charvin.

Abdominal pain of a spasmodic character accompanied by vomiting, but without diarrhea, the maximum pain traceable to the kidney or along the ureter, dysuria, rapid recovery from the attack and that followed by passing gravel, leaves little else to complete the diagnosis. In infected calculus, pus and very little blood may overshadow symptoms of its presence.

Rectal examination may be useful in the diagnosis of bladder stone, also ureteral stone. Fagge and Robinson are each quoted by Rafin as having made diagnoses of calculus in the ureter by this method.

Ureteral catheterization in the infant is practically impossible. It is difficult to say at what age such instrumental procedures begin to be practicable. Rafin separated the urine in a little girl of 6 months.

If the radiograph is important as an agent in diagnosis on the adult, it is of even greater importance in the diagnostic endeavor on the infant. Here it has served to point out many errors which occurred in diagnosis

before, and it should be advised in all suspected cases. Hartman speaks of a case in which a radiograph was not made and the surprise was great at finding stone at autopsy. In our day the diagnosis should not be considered complete without a good radiograph. It may not always be complete with the radiograph. It is said by Tenney that a positive plate is more dependable, however, than a negative one, although there is a small degree of error in both negative and positive. In ninety-three of Leonard's cases, five failed to find stone. In 233 of his cases with negative diagnoses, a stone was found at operation, or passed, in four. Carl Beck advises radiographing the kidney region in addition to the vesical when vesical calculus is suspected. It is very desirable that a radiograph be obtained which shows clearly all kidney, ureteral and bladder regions, i. e., the total urinary system. In infants and young children two plates should be sufficient and usually one large plate will suffice. In case two are used, one should show both kidney and upper ureteral regions, the other should include the bladder and lower ureteral regions. The necessity of an instantaneous exposure in the case of a crying and wriggling infant needs no elaboration. Immobility of respiration is practically impossible. The dorsal position is found to be the best. The thighs should be flexed, even to a right angle, if necessary, in order to eliminate the "saddle-back" and to permit contact of the back with the plate. A purge is advisable before the radiograph is made. The table should be warm to lessen trembling.

The knowledge of the localization of stones simultaneously in different parts of the urinary tract is very important. A direct relationship exists between the multiplicity of localization and gravity of operation. Multiplicity of localization also darkens the prognosis.

#### PROGNOSIS

Charvin states that lithiasis in the adult may be traced back to infancy. This would lead one to believe that the immediate prognosis is good. Gravel, it is true, is generally of long duration. (See Table 3.)

In Table 3 it will be seen that the interval of time between the date of onset, or at which symptoms pointing to disturbances in the urinary tract occurred, and the date of admission, or such time as the patient presented himself for treatment, varies within wide limits. In the thirty-eight cases tabulated it will be seen that the interval above mentioned ranged from six months or less up to forty-one years. This is in evidence of the tendency to chronicity with respect to urinary stone. And here we return to the principle of "survival of the fittest." H. Joseph has made a very praiseworthy study of forty cases *post mortem*, in which stones were found in the kidneys or elsewhere in the urinary tract. None of these were diagnosed during life. Of this material, 65 per cent. were

TABLE 3.—TO SHOW IN THE CASES OF CHARVIN, MONSSEAUX AND PORTER  
THE INTERVAL OF TIME BETWEEN FIRST ONSET AND TIME OF ADMISSION;  
ALSO, WHERE STATED, SIZE OF STONE RECOVERED

Case	Age on Admission, Years	Age at Onset, Years	Interval, Years	Remarks
Charvin				
4	3½	?	?	Autopsy: Right kidney crammed with small stones. Largest were 12 x 8 mm. (½" x 3/10").
9	10	8	2	Urate calculi.
11	15	14	1	Stone size small pea.
12	12	9	3	
13	6	3	3	Stone wt. 8 gm.
16	10	?	...	¾" x ¼"; cylindrical.
17	9	4	5	
18	6	¾	5	
19	11	9	2	Stone 8 x 6 x 4 cm. in size.
20	10	2	8	
21	12	11-12	½	
22	5	4½	½	
29	7	4	3	
32	14	12	2	
35	4	4	0	
37	15	15	0	
39	4	3	1	Stone wt. 33 gm.
40	7	?	?	Stone wt. 18 gm.
41	11½	1	10	
42	11½	3	8	
43	9	6	3	
Adult Cases				
46	16	10	6	Stone wt. 25 gm.
47	18	12	6	
48	19	15	4	
49	19	7	12	
50	20	12	8	
51	24	4	20	
52	24	6	18	
53	46	5	41	
Monsseaux				
1	19	5	14	
2	21	12	9	
3	31	10	21	
4	33	15	18	
5	24	12	12	
6	29	7	22	
7	43	8	35	
8	48	13	35	
Porter Case				
..	4	½	3½	Stone wt. 3.9 gm.; size 7/8" x 3/8".

bilateral cases. I have arranged some of his statistics in tabular form, as will be shown in Table 4.

The evident predominance of bilateral involvement, as shown by Table 4, bears out Rafin and Charvin in that the prognosis becomes more somber with multiplicity of involvement. On 76 observations at autopsy Legen found thirty-six (nearly 50 per cent.) cases of bilateral calculi. Kuster, who bases his study on clinical facts, arrives at the proportion of 11.78 per cent. bilateral stones. Leroy found 22 per cent. of bilateral renal or ureteral stones. Of the cases operated on by Rafin he found four bilateral cases, or 8.8 per cent. A highly important lesson to be drawn from the preceding information, therefore, considering the high mortality of cases of multiple involvement, is that the cases must be discovered and treated earlier, before destruction of kidney substance progresses to cripple the organ or infection becomes a complication.

Cuturi determined from his animal experiments three very potent conclusions: (1) *B. coli* reaching the healthy kidney by way of the bloodstream causes no lesion. It simply causes bacteriuria. (2) *B. coli* in the kidney complicated by calculus provokes pyelonephritis and pyonephrosis. (3) Experimentally, by separation or ligation of the rectum for twenty-four hours, one obtains a pyelonephritis by the passage of *B. coli* to the kidney by way of the blood, after ligation of the ureter. If, therefore, the above conclusions apply to the human, an individual harboring a primary stone runs a greater chance of secondary infection when constipation exists.

When, after much trouble, the kidney ceases the struggle and there occurs a complete disappearance of symptoms, the relief affords a sense of false security, for in the words of Rafin: "*Ce silence sera le signe de la mort de l'organe*" — the silence will be the sign of the death of the organ.

Ureteral stone as well may occasionally take on a serious aspect if it becomes incarcerated. Guisy reports the case of a little girl of 12 in whom a mixed urate and phosphate stone became lodged in the ureter and caused a lumbar abscess, necessitating incision and removal of the stone.

A large number of Monsseaux's patients, many of them older children, were subjects of migraine headache, eczema, epistaxis and conjunctivitis; some were asthmatic, some had urticaria at intervals, others had transient articular manifestations without fever or swelling, but some pain. In his opinion, if the infant is without hereditary taint, the calculus of an accidental sort, due to alimentary disorders and poor hygiene, etc., the prognosis is not too severe and the patient's chances are good under better conditions. If, on the contrary, the infant is an inveterate arthritic subject, with bad heredity, presenting at the same



TABLE 4.—COMPILED FROM JOSEPH'S FORTY AUTOPSY CASES IN INFANTS TWO YEARS OR UNDER, TO SHOW THE RELATIVE FREQUENCY WITH WHICH URINARY STONE AND COMPLICATING HYDRONEPHROSIS ARE ASSOCIATED WITH INTERCURRENT DISEASES IN OTHER REGIONS OF THE BODY

Post-Mortem Findings	Nephrolithiasis			Hydronephrosis				
	Left Kidney	Right Kidney	Bilat.	Left	Right	Bilat.	Bladder Stone	Totals
Atrophy .....	1	2	2	1	...	...	...	6
Tracheitis .....	...	...	1	...	...	...	...	1
Enteritis .....	2	4	8	2	1	...	...	17
Otitis media .....	1	1	2	...	...	...	2	6
Gastro-enteritis .....	...	...	2	...	...	...	...	2
Abscess submax. gland...	...	...	1	1	...	...	...	2
Cardiac dilatation.....	1	1	4	1	...	...	...	7
Bronchitis .....	1	...	1	1	...	...	...	3
Edema pia mater.....	...	...	1	...	...	...	...	1
Hyper. mes. lymph-nodes	...	1	3	...	...	1	...	5
Rachitis .....	...	2	4	...	...	...	...	6
Hemorr. pia mater.....	...	...	1	...	...	...	...	1
Hydrothorax .....	...	1	...	...	1	...	...	2
Lobar pneumonia .....	...	2	5	1	1	...	...	9
Ascites .....	...	1	...	...	1	...	...	2
Bronchopneumonia .....	1	2	7	...	...	1	...	11
Meningitis .....	...	...	2	...	...	...	...	2
Hydrocephalus .....	...	2	2	1	...	...	...	5
Colitis .....	...	1	2	1	...	...	...	4
Cystitis .....	...	...	1	...	...	...	...	1
Abscess mult. cutaneous..	...	...	1	...	...	...	...	1
Osteochondritis .....	...	...	1	...	...	...	...	1
Miliary tuberculosis.....	...	...	1	...	...	...	...	1
Intestinal tuberculosis...	...	...	1	...	...	...	...	1
Pulmonary tuberculosis..	1	...	1	...	...	...	1	3
Meningeal hemorrhage...	...	1	1	...	...	...	...	2
Diphtheria .....	...	1	1	...	...	...	...	2
Carbuncle and furuncu-	...	...	...	...	...	...	...	...
losis .....	1	...	1	...	...	...	...	2
Pararectal abscess .....	...	...	1	...	...	...	...	1
Totals .....	9	22	58	9	4	2	3	107

It will be seen from this table that diseases of an infectious nature occur in association with calculus and hydronephrosis 70 times out of 107, or 65 per cent. Enteritis and gastro-enteritis are associated with urinary stone and hydronephrosis 19 times; rachitis 6 times; lobar and bronchopneumonia 20 times.

Respiratory tract associated with stone or hydronephrosis 29 times.  
Alimentary tract associated with stone or hydronephrosis 25 times.  
Systemic diseases associated with stone or hydronephrosis 15 times.  
Nervous system associated with stone or hydronephrosis 11 times.  
Glandular system associated with stone or hydronephrosis 7 times.

time habitual manifestations of the diathesis, is subject to migraines, epistaxis, gastro-intestinal trouble or joint-pains, tends to obesity, in a word, is not uremic or arthritic on occasion, but by temperament, and is rebellious to treatment and subject to recurrences, the outlook is not so good.

#### TREATMENT

One is confronted in the older literature with the various methods of dietary and medical treatment. In the more recent literature the surgical treatment of urinary stone finds more frequent discussion. Unless the calculi are discovered earlier and removed promptly the mortality will remain high. Calculi in the infant kidney or ureter should be expelled or relieved surgically. The destruction of kidney substance, the blocking of a ureter, the danger of infection, are matters for grave consideration when a calculus is the impeding object. Delay, as suggested by Charvin, enhances the operative risk in that nephrectomy may be necessary in the late stage, where nephrotomy would have sufficed in the early stage. Statistics favor operative relief. Jeanbrau believes the danger of the presence of stone in infants is greater than surgical interference. Sumpter reports a case of bladder calculus in a boy baby 22 months old, removed suprapubically with good result and no recurrence. Porter reports the case of a baby girl first seen at the age of 6 months. She had had colic for two years or more, passing fully a drachm of calculi of small size. Operation was done at 3 years 10 months, and a 60-gram calculus recovered suprapubically. Good recovery followed.

The very instructive case recorded by Aleksinski is worthy of citation here:

The boy was first seen at 7 years, his complaint being painful micturition. At two he had "nervous fits" which were never accurately diagnosed; at five pleurisy with effusion; at 6 he began to have painful micturition, a thin stream and frequently interrupted. The urine contained pus and blood. The temperature ran as high as 104 F. A diagnosis of vesical calculus was followed by suprapubic removal of the stone. A month later his old symptoms reappeared. Urine 1.007, daily quantity 1,500 c.c., acid, turbid, pus and blood cells, oxalates and mucus. Albumin present. Bacteriological examination showed *B. coli*. Radiograph showed shadows in both kidney regions. Nephrectomy on the right side brought forth three stones the size of walnuts. The urine presented no improvement and three weeks afterward at operation the left kidney yielded four stones. Following this last operation he sat up on the eighth day and was discharged on the seventeenth day. Seven months afterward he was well and the urine was normal.

As in the case just cited, where extensive involvement exists it is an accredited procedure to operate in successive stages. Attention to the bladder stones with neglect of the kidney condition is generally a grave injustice to the patient. The wisdom of finding out beforehand, if possible, the localization of stones simultaneously in different parts of

the urinary tract is therefore very important. In eleven operations done by Rafin on infants and children, five were for aseptic stone; six infected. Two had multiple operations. Ten were nephrotomies. Three were nephrectomies. A pyelotomy was done in one case. Recovery occurred in all of the cases.

Such information as it is possible to obtain by means of the cystoscope and the ureteral catheter in adult cases is seldom if ever possible in the child or infant, and this augments the responsibility of doing a nephrectomy. When dealing with the adult, part of the responsibility is shared by the cystoscopist, who has decided before operation, the adequacy of the other kidney. With the infant or small child the weight of responsibility of removing a diseased kidney rests almost entirely on the operator. Examination of both kidneys through lumbar incisions before deciding the operative procedure may save an occasional fatality.

#### CONCLUSIONS

1. In the past, urinary lithiasis, especially renal, has been accompanied by a high mortality.

2. Of the cases of renal calculus in children 5 years or under, more than 90 per cent. were 2 years or under, and practically all of those were *post mortem* cases.

3. There is a paucity of case reports of renal stone in infants discovered and treated surgically during life.

4. Calculi discovered in older children or in adult life frequently originate in infancy or childhood.

5. The finding of sand or gravel in the infant urine is sufficient reason for advising radiographic examination of the urinary tract.

6. Gravel may be of long duration, ranging from six months or less up to forty-one years.

7. Diseases of an infectious nature occur in association with calculus and hydronephrosis 70 times out of 107, or 65 per cent.

8. Diseases of the respiratory tract are associated with urinary stone or hydronephrosis most often.

9. Bilateral or multiple calculi in the urinary tract offers a condition with an unfavorable prognosis.

10. To better the prognosis, cases must be discovered and patients treated earlier, before destruction of kidney substance progresses to cripple the organ, or infection becomes a complication.

11. Surgical interference is an accredited procedure. When multiple involvement exists, operation in successive stages may be done.

12. Greater responsibility is attached to nephrectomy in the infant by reason of the difficulty of ascertaining the functional capacity of the opposite kidney.

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## THE GASTRIC SECRETION OF INFANTS AT BIRTH \*

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There has been no lack of investigation of the gastric secretion of infants. Shortly after the stomach tube was devised by Kussmaul it was carried into the field of pediatrics, first for therapeutic measures and considerably later for physiologic studies. In spite of many years of varied work in this field, it must be admitted that we have not progressed far in our knowledge of the physiology of gastric digestion. Numerous causes may be assigned for this slow progress. One of the main obstacles to a scientific study of secretion — the phenomenon which interests us particularly at this time — has been and remains the fact that the acid juice rapidly enters into combination with the milk food, so that it becomes impossible to judge accurately of its quantity or of its quality. It is this variable factor which accounts for the wide discrepancies in the reports on this subject, for the differences of opinion regarding the importance of hydrochloric acid at this time of life, and for the total lack of normal values for the gastric secretion of infants.

The present study, which was carried out in conjunction with an investigation of icterus neonatorum and its relation to bile secretion,<sup>1</sup> *concerns itself merely with infants during the first few hours of life, who have never been given any food.* Thus the disturbing and complicating factor of the interaction of the gastric juice and of the food does not have to be considered. Quite apart from the question of whether a study from this limited point of view might prove of clinical value, it seemed worthy of investigation for its physiologic interest, because, as we have said, from its very nature it eliminated the food factor and reduced a complex subject to its simplest terms. The questions of suitability of diet, of previous gastric derangement, or of intercurrent illness, in fact, all complicating factors, excepting those possibly congenital in origin, were also naturally excluded.

Our study includes a gastric examination of fifty-five infants, varying in age from one-half hour to eighteen hours. Such a considerable number of tests must not be regarded as indicating a lack of uniformity in the results. They were carried out to this extent because, as has been

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\* Presented in abstract before the Society for Experimental Medicine and Biology, February, 1912.

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1. Hess, A. F.: AM. JOUR. DIS. CHILD., 1912. iii. 304.

mentioned, this work was performed in conjunction with another experimental study — that of the duodenal contents of the new-born. Indeed, attention was first directed to this question in the course of investigations by means of the duodenal catheter.

A review of the literature of the gastric secretion of infants revealed practically nothing on this phase of the subject. The only published account of examinations of the contents of the stomach of new-born (unfed) infants are two by Leo,<sup>2</sup> and a solitary test made by Szydlowski<sup>3</sup> many years ago. Some post mortem reports were found: Zweifel,<sup>4</sup> in 1874, demonstrated the presence of pepsin in the gastric mucosa of the new-born, and Langendorff,<sup>5</sup> a few years later, found this ferment in the mucous membrane of a 4-months-old fetus.

As the subject seemed worthy of further and closer investigation, it was entered on in detail to determine the presence of free hydrochloric acid, of pepsin, of rennin, of gastric lipase; the degree of secretion and its duration; its relation to the general physical condition of the infant; the relation of the hydrochloric acid secretion to tonicity of the pylorus; its relation to the pancreatic secretions; its relation to later gastric secretion, at a period when the babies had been fed. Finally an attempt was made to interpret the nature of the secretory stimulus in the light of our own tests and of present physiologic viewpoints.

We have summarized the results in tabular form (Table 1). A glance at this table shows that in almost every test hydrochloric acid was found; it was lacking in only one out of 52, and was found in the free state in all but two. The infants varied in age from one-half hour to eighteen hours, and in no instance had received any food or water. The method of obtaining the gastric contents differed from that usually employed only in the use of a glass aspirating bulb.<sup>6</sup> There is no doubt that we did not, at all times, completely empty the stomach. Bearing this in mind, it is the more interesting to find that these new-born infants showed as much as 8 to 10 c.c. of highly acid gastric juice, containing a large amount of free hydrochloric acid. The juice was clear or slightly turbid, somewhat viscid, due to an admixture of mucus, which is secreted freely in this early period, and contained a varying amount of saliva. The saliva is not included in the figures giving the total quantity; as far

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2. Leo, H.: Berl. klin. Wchnschr., 1887, xxiv.

3. Szydlowski, Z.: Jahrb. f. Kinderh., 1892, xxxiv, 411.

4. Zweifel, O.: Untersuch. ueber d. Verdauungsapparat d. Neugeb., 1874.

5. Langendorff, O.: Arch. f. Anat. u. Physiol., lxxix, 95.

6. It is unnecessary to describe this simple instrument, as it has been reproduced in recent articles in connection with an account of duodenal catheterization (*AM. JOUR. DIS. CHILD.*, 1912, iii, 133; *Arch. Int. Med.*, 1912, x, 37.) It has been found exceedingly serviceable in emptying the stomach, for although even with this aid the gastric contents cannot always be completely evacuated, it enables us to obtain a far larger quantity than when aspiration is not employed.

TABLE 1.—GASTRIC SECRETION IN THE UNFED NEW-BORN

Case	Hours Old	Gastric Juice, c.c.	Free HCl	Comb. HCl	Remarks
1	1½	2.0	++	....	Pepsin rennin. 14 c.c. in one hour. 17 c.c. in 1 5/6 hours. (See text.)
2	4½	10.0	+++	....	
3	4½	8.0	60	....	
4	4	8.0	+++	....	
5	5	3.0	+++	....	
6	2	5.0	+++	....	
7	1¼	3.0	+++	....	Liapase 0.4
8	¾	?	+++	....	
9	10	1.5	22	....	
10	6	1.0	15	....	
11	2⅔	8.0	20	32.0	
12	5	2.0	+++	....	
13	5	6.0	19	37	
14	17½	1.0	+++	....	
15	12¾	2.0	+++	....	
16	5½	2.0	17.5	17.5	
17	7	2.8	45	36	
21	2½	2.0	+++	....	Lipase 0.3.
22	2	1.0	+++	....	
23	8	2.0	+++	....	
24	5⅓	3.0	+++	....	
25	7½	1.0	+++	....	
26	12	1.0	+++	....	
27	12	1.0	+++	....	Lipase 0.2 rennin
28	18	2.0	+++	....	
29	4	3.0	35	50	
30	1½	4.0	+++	....	
31	9	2.0	+++	....	
32	14	5.0	+++	....	Saliva marked.
33	5¾	0.5	++	....	
34	5½	0.5	0	....	
35	5	0.25	++	....	
36	5½	0.5	+++	....	
37	15	0.5	++	....	Rennin pepsin.
38	12	1.0	+++	....	
39	5	3.0	+++	....	
40	6	5.0	+++	....	
41	3	2.0	++	....	
42	7	0.3	++	....	
43	3	8.0	+++	....	
44	5½	12.0	+++	....	
45	5½	0.3	++	....	
46	1½	1.5	++	....	
47	3	1.0	++	....	
48	10	?	+++	....	Pepsin rennin.
49	4	5.0	120	....	
50	2½	1.5	+++	....	
51	2½	2.5	+++	....	
52	7¼	5.0	35.0	37.5	
53	...	1.0	++	....	
54	10	?	0	+	
55	9	2.0	+++	....	



as possible it was removed from the surface of the fluid, so as not to interfere with the acidity tests. For the test of hydrochloric acid Congo paper was used in the clinic, and Toepfer's solution as an indicator for the titration in the laboratory; for the test of combined hydrochloric acid alizarin was employed. We do not wish to insist on the quantitative accuracy of these tests.<sup>7</sup> However, they are probably not too high. For from a quantitative standpoint, all intercurrent disturbing factors, such as admixture of mucus or of saliva, tend to lower the figures for free hydrochloric acid from their level rather than to raise them. Moreover, the figures would seem more accurate than those obtained from older babies on account of the absence of peptones and albumoses which interfere with the activity of the test indicators. We may therefore state not only *that very soon after birth there is free hydrochloric acid, but that there is a considerable amount of this acid in the unfed infant's stomach*. Rennin and pepsin are also present at this time; as a test for the former, milk was used, and for the latter, coagulated egg-white. No quantitative estimation of these two ferments was attempted; their presence in the gastric juice was confirmed several times, and their enzymatic action definite and conclusive. As regards the source and the nature of the lipase, noted in the table, there may be some question. We believe that it is of gastric and not of pancreatic origin, because it was found in fluid which contained no trypsin;<sup>8</sup> Sedgwick<sup>9</sup> found it in the stomach of an infant at the age of 2 weeks, and Ibrahim<sup>10</sup> in a 6-months-old fetus.

The secretion of the gastric juice and the elaboration of the ferments were not brought about by the passage of the stomach-tube. This was evident from the fact that the juice was obtained immediately on passing the tube. In order to test the contrary hypothesis, in several cases the catheter was inserted with the greatest dispatch. This did not lessen the amount of gastric juice obtained. According to Pawlow,<sup>11</sup> the gastric mucosa does not react to mechanical stimulation. Moreover, whatever the nature of the stimulus, all physiologists are agreed that a latent

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7. In some instances but 1 or 2 c.c. of fluid was available for titration, so that error undoubtedly resulted in the course of the necessary multiplication of the figures. However, the fact that in several instances a repeated test showed a repetition of the high acidity argues for approximate exactness. This fact is well brought out by the figures in the case of prolonged gastric secretion which are cited below in full. Moreover it will be noticed that, in general and with slight exception, the amount of hydrochloric acid was found to be excessively high.

8. For the lipase tests, neutral ethyl butyrate was used as in the studies of pancreatic ferments (Hess, A. F.: *AM. JOUR. DIS. CHILD.*, 1912, iii, 205.) The figures in Table 1 denote titration against 1/20/n NaOH.

9. Sedgwick, J. P.: *Jahrb. f. Kinderh.*, 1906, lxiv, 194.

10. Ibrahim, J.: *Ztschr. f. Biol.*, liii, 201.

11. Pawlov, I. P.: *The Work of the Digestive Glands*, second English ed., 1910.

period must elapse before the glands respond. As the result of experiments on animals, Cohnheim<sup>12</sup> places this latent period of the gastric mucosa, following psychic stimuli, at about seven minutes. Pawlow<sup>11</sup> gives the same latent period for the reaction to food. In view of experimental as well as of clinical evidence, it therefore seems certain that in our cases the gastric juice was in the stomach before the passage of the catheter, and was not the result of mechanical stimulation. We shall consider later in greater detail the nature of the secretory stimulus after noting some clinical experiments.

Having assured ourselves that the secretion of hydrochloric acid in new-born infants is the rule, almost without exception, we undertook a more precise investigation of the question. One of the first subjects of inquiry was as to the continuance of the secretion — whether hydrochloric acid and the ferments are in the stomach at the beginning of the test only, or whether they can be obtained throughout long periods. Many tests were made to elucidate this question. We report a few in detail:

#### REPORT OF EXPERIMENTS

CASE 6.—Nov. 4, 1911. Baby K., 2 hours old. Weight 7 pounds, 9 ounces. Experiment lasting one hour and fifty minutes.

Specimen 1, aspirated after five minutes; 6 c.c. cloudy fluid; moderate amount of saliva; free HCl=56. (Five c.c. tested.)

Specimen 2, aspirated after 10 minutes; 2.5 c.c. cloudy fluid; moderate amount of saliva; free HCl=50-55. (Two c.c. tested.)

Specimen 3. Catheter withdrawn; reintroduced after ten minutes' interval; aspiration continued intermittently for fifteen minutes. Three c.c. fluid; marked saliva. Free HCl=30. (Three c.c. tested.)

Specimen 4. Catheter withdrawn; reintroduced after twenty-five minutes' interval, and aspiration continued intermittently for fifteen minutes; 25 c.c. fluid; slight saliva. Free HCl=50. (Two c.c. tested.)

Specimen 5. Catheter reintroduced after fifteen-minute interval; aspiration for fifteen minutes; 3 c.c. fluid; slight saliva. Free HCl=46. (Three c.c. tested.)

*Epicrisis.*—In a test of an hour and fifty minutes 17 c.c. of highly acid gastric juice was obtained from a new-born infant. No decrease in the amount or strength of HCl secretion was evident during that period.

CASE 30.—Dec. 4, 1911. Baby B., 1½ hours old. Weight 6 pounds, eight ounces. 3 p m., No. 14 F. catheter passed. Gagging slight; 4 c.c. viscid, Congo +++ fluid obtained; saliva marked.

3:05. Catheter reinserted; 3 c.c. Congo +++ fluid. Saliva.

3:15. Inserted into esophagus; saliva and neutral fluid obtained.

3:25. Stomach entered; very slight saliva.

3:30. Stomach contained small amount of Congo +++ juice and saliva.

3:40. Two c.c. Congo +++ fluid with saliva. Baby quiet. Catheter kept steady and not moved about.

3:42. Duodenum easily entered; dry tap after twelve minutes.

3:54. Good retraction test as reentered stomach. About 1 c.c. clear Congo + fluid. No saliva.

3:55. Reentered duodenum. Dry tap after five minutes.

12. Cohnheim. O., and Soetbeer, F.: *Ztschr. f. physiol. Chem.*, 1903, xxxvii, 467.

4:00. Good retraction test. About 2 c.c. Congo +++ fluid in stomach. No saliva.

*Epicrisis.*—In a test lasting an hour, free HCl was continuously found in the stomach.

CASE 39.—Dec. 28, 1911. Baby U., 5 hours old.

11:55 a. m. No. 14 F. catheter passed. In two minutes 3 c.c. Congo +++ fluid; moderate saliva; pharynx reflex increased; tube washed.

12:00 noon. Catheter introduced into duodenum; marked gagging.

12:10 p. m. Good retraction test; thick mucous. Congo negative; fluid aspirated.

12:15 p. m. Reintroduced into duodenum and retained in place.

12:27 p. m. Retracted into stomach; 0.5 c.c. Congo +, Litmus ++ fluid. Catheter withdrawn.

12:30 p. m. Reentered stomach; 2.5 c.c. Congo + fluid; some saliva.

12:35 p. m. Reintroduced into stomach; 0.5 c.c. Congo ++ fluid.

*Epicrisis.*—In a test lasting forty minutes, free HCl was repeatedly aspirated from the stomach.

It is evident, therefore, that whatever may be the nature of the stimulus, not only is hydrochloric acid present in the stomach of the new-born, but that *it may be secreted almost uninterruptedly for long periods (hours) quite independent of the ingestion of any food.*

Reference has been made to the fact that in one instance there was an absence of hydrochloric acid. It was not until the thirty-fourth case that a result of this nature was encountered.

CASE 34.—Dec. 18, 1911. Baby F., 5½ hours old; weight 8 pounds, 8 ounces.

2:30. No. 14 F. catheter introduced; small amount neutral Congo negative fluid; slight blood and saliva; pharynx reflex almost absent.

2:35. Reintroduced. Congo negative; litmus negative.

2:38. Reintroduced; 0.5 c.c. fluid, Congo negative; litmus negative.

2:45. Reintroduced; 0.5 c.c. fluid, Congo negative; litmus negative.

2:55. Entered duodenum easily. Dry tap after twenty minutes.

3:08. Entered stomach; 0.5 c.c. saliva neutral, Congo negative fluid.

*Epicrisis.*—Absence of hydrochloric acid and neutral reaction of stomach contents in five successive tests during a period of thirty-eight minutes.

CASE 34.—Second test.

Dec. 26, 1911; 8 days old; nursed 1¼ hours previously.

3:17. Five c.c. milk aspirated. Congo negative.

3:27. Catheter passed again. Entered duodenum easily.

3:42. Retracted into stomach. Fluid contained saliva, mucus, Congo +.

3:45. Passed into duodenum; 0.6 c.c. fluid containing bile.

4:10. Reintroduced into stomach. During five minutes Congo negative.

CASE 34.—Third test.

Dec. 27, 1911; 9 days old; nursed shortly before test.

2:54. No. 14 F. catheter passed. Two ounces of milk obtained. Congo negative, litmus +.

3:00. Duodenum easily entered.

3:10. Retracted into stomach. Congo negative, litmus +.

3:13. Reintroduced. Congo negative.

*Epicrisis.*—Retests when the infant was 8 and 9 days old showed HCl present but deficient.

Among the fifty-five infants tested, this was the only one in which there was complete absence of hydrochloric acid at birth. The two later



tests, detailed above, show that acid was being secreted, although in small amount. We are evidently dealing here with a functional disturbance, an anomaly of secretion which may be termed *congenital hypochlorhydria*. Another case (Case 54) should be mentioned in this connection, as it was the only other one in which free acid was not found at birth. However, as the gastric fluid was acid, and the test lasted but five minutes, we must consider that there was merely a deficiency of hydrochloric acid in this case. On the other hand, instances were also met with in which there was a comparative *hypersecretion* of hydrochloric acid; the case (Case 6) cited above as a marked instance of continued secretion may well be brought under this category. We are unable to state the significance of these abnormal variations of secretion. It would be interesting to know how long they persist, or of their possible association with similar conditions in later life.

It is not proposed to consider the gastric secretion of infants who have been put to the breast. However, a few words in this connection may not be amiss, as we carried out a gastric examination on a large group of infants under 10 days of age, incidental to the study of icterus neonatorum. Furthermore, the opportunity was frequently afforded of examining the same infant, first when it was unfed, and later in the course of the first week or two of life. The following case brings out sharply a comparative test of this kind:

CASE 39.—First test; infant 5 hours old.

11:55. Catheter passed. In two minutes about 3 c.c. Congo +++ fluid. Moderate saliva.

12:00. Reintroduced. Easily entered the duodenum; mucus.

12:15. Reintroduced into the duodenum.

12:27. Retracted into stomach. Congo +, litmus ++ fluid.

12:30. Passed into stomach again; 2.5 c.c. Congo + fluid; saliva.

12:35. Reintroduced into stomach; 0.5 c.c. Congo ++ fluid.

Second test; infant 6 days old.

3:38. Catheter passed. About 1 ounce fluid, Congo negative.

3:40. Passed pylorus.

3:48. Retracted into stomach; Congo negative fluid.

3:50. Reinserted into duodenum; thick mucus.

4:01. Reinserted. Some mucus, neutral, Congo negative.

4:05. No. 15 F. catheter inserted.

4:25. Withdrawn; alkaline mucus. Congo negative; material in stomach.

*Epicrisis*.—Test when 5 hours old (unfed) showed marked hydrochloric acid in stomach and continued secretion for forty minutes. Test when 6 days old showed no hydrochloric acid during forty-five minutes.

It is difficult to explain the fact that in this case and in some others there was a greater secretion before the child had been fed than a few days later. We should have expected to find quite the contrary condition, when we consider that at the time of the first test there was an absolute lack of stimulus from food, which is regarded as a powerful gastric secretagogue. We do not refer merely to the fact that more gastric juice



was found in the stomach soon after birth than later. This might be accounted for by the supposition that it was the product of many hours of secretory activity. But here is an instance in which the stomach, in the case of an unfed infant, continued to secrete acid juice for forty minutes, whereas in the same infant, after it had been nursed for some days, acid secretion was absent or lacking — in a test lasting for a longer period. Evidently the stimulus to gastric secretion is at times more potent at birth than during the early days of infancy.

#### NATURE OF STIMULUS OF HYDROCHLORIC ACID PRODUCTION

The consideration of the nature of the stimulus of the hydrochloric acid secretion proved a most interesting part of this study. It seemed adapted to investigation, although we realized at the outset that it would be hampered by the limitations which surround all physiologic studies in human beings. On the other hand previous studies of this nature are open to the criticism that they have been carried out on animals, and that their deductions have been presumed to apply to human physiology. But before proceeding further, it may be well to outline the present viewpoint in regard to the normal mechanism of the secretion of gastric juice. Let us follow a standard text-book of physiology.<sup>13</sup> In the first place, it is considered a proved fact as the result of Pawlow's experiments, that "mechanical stimulation of the gastric mucous membrane has no effect on the secretion of the tubules." There are three steps in the mechanism of secretion: (1) The psychical secretion, for which the afferent stimuli originate in the mouth and nostrils, and the efferent path through the vagus nerve; (2) the secretion from secretagogues contained in the food; (3) the secretion from secretagogues contained in the products of digestion. The manner in which the secretagogues act cannot be positively stated. Recently Edkins<sup>14</sup> has suggested, as the result of experiments, that a gastric secretin is formed through the interaction of the food and of the mucous membrane of the pylorus; that this substance is absorbed by the blood, and, acting as a hormone or messenger, is carried to the gastric glands, stimulating them to secretion. According to these views, as given by Howell, we must distinguish between a nervous secretion due to the action of the secretory fibers in the vagus, and a chemical secretion due to the chemical stimulation of secretagogues or of hormones. Viewed from this physiologic standpoint, how are we to interpret the fact that (a) hydrochloric acid and gastric ferments are found in the stomach soon after birth, and (b) that the new-born infant, although unfed, continues to secrete them?

13. Howell, W. H.: *Text-Book of Physiology*, 1911, p. 763.

14. Edkins: *Jour. Physiol.*, 1906, xxxiv, 133.

It is at once evident that prevailing physiologic views do not account for (a) the secretion of hydrochloric acid immediately after birth. For the exciting stimulus can be neither psychical, "a term which implies that the reflex must be attended by conscious sensations," nor, as we are considering unfed infants, can it be chemical, a secretagogue formed or stimulated by the food.<sup>15</sup> Although this is evident, and it is clear that some other mechanism must exist to account for the secretion at this time of life, we are not prepared to offer a new hypothesis. There are some factors, however, associated with this problem which are worthy of further consideration and discussion. It will be seen from the table (Table 1) that a juice containing hydrochloric acid was obtained as early as one-half hour after birth, and that it was frequently found within the first two hours of life. This secretion may be regarded as either prenatal or postnatal in origin. If the latter view be accepted, we may regard it as in some way connected with the changes in the respiratory and in the circulatory systems, which come about at the time of birth. On the other hand, it may well be that the juice was secreted before birth as the result of an unknown mechanism different from that which obtains in extra-uterine life. This conception of the prenatal secretion of gastric juice, containing hydrochloric acid and ferments, at once raises the question of a fetal gastric digestion, an interesting but at present a purely speculative field.<sup>16</sup>

Let us now turn to the other phase of the problem (b), the continued secretion of gastric juice by the unfed infant. We have stated that likewise this secretion can be neither of reflex origin, that is to say, psychic, nor of chemical origin, namely, due to a secretagogue. In the course of the many tests on new-born babies, observations were noted regarding the effect of mechanical irritation of the stomach, the secretion of saliva, the sucking of the tube by the infant, and other factors, in order to ascertain whether any parallelism could be discovered between these possible stimuli and the degree of gastric secretion. It should be remembered that throughout extended tests we obtained gastric juice containing a high degree of hydrochloric acid. The instances which have been cited above, in which the juice was obtained for twenty minutes,

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15. In this connection mechanical stimulation may be left out of consideration, as in many instances the catheter was rapidly passed and the gastric contents obtained immediately on its introduction. A latent period of less than a minute between a mechanical stimulus and profuse secretion is inconceivable and contrary to all experience.

16. Although analogies cannot serve as arguments, we may recall in this connection the prenatal secretion of the liver (bile), of the sebaceous glands (vernix caseosa), and of the glands of the vagina. It should also be considered whether the infant in utero does not perhaps swallow liquor amnii oftener than is generally believed, and whether this fluid may not act as a stimulus to gastric secretion.

forty minutes, or even for an hour or more are not exceptions. It seemed as if we would have ample opportunity to study this question. However, in most instances the phenomena were interwoven and could not be isolated; the infant which sucked the catheter had also a flow of saliva, or, for example, where mechanical irritation was attempted, some secondary factor could not be rigidly excluded. Nevertheless, some cases are worthy of note.

It has been suggested that the saliva may act as a stimulus to the secretion of gastric juice. From this point of view it is significant that, although at times both salivary and gastric secretion were profuse, in the only case (No. 34, cited above in detail) in which no hydrochloric acid whatsoever was found, there was an average quantity of saliva. In another instance (No. 35) hydrochloric acid was obtained on the introduction of the catheter, but could not be found later in the test, although salivation was marked and aspiration was continued at intervals for half an hour. We select these two cases for illustration as they seem conclusive, unless we are to consider them as exceptions to a rule. If not, we must conclude that the saliva does not constitute the essential gastric stimulus in the new-born.

We were not able to control the gastric secretion by mechanical stimulation, that is, to increase it by moving the catheter about in the stomach, or to decrease its flow by maintaining the catheter at rest. But it should be added that as each case differed in the amount of gastric secretion, it would be unwise to draw deductions from individual instances. It seemed as if the secretion of mucus rather than of hydrochloric acid was stimulated by mechanical irritation.

#### INFLUENCE OF SUCKING ON GASTRIC SECRETION

From the beginning our attention was directed to the influence of sucking on gastric secretion. Some years ago Pfaundler<sup>17</sup> studied this question clinically, and suggested that there is more acid secreted when infants nurse actively than when they are fed passively. The lack of normal standard for gastric juice rendered his figures inconclusive. Cohnheim and Soetbeer<sup>12</sup> investigated this subject on very young puppies, on which an esophagostomy and a gastrostomy had been performed; however, the animals did not live long. The authors came to the somewhat hypothetical conclusion that secretion is a congenital reflex. We approached the question clinically by having the infant suck on a catheter passed as far as the esophagus; this allowed the saliva to be continuously aspirated as it flowed down from the pharynx, but did not entail mechanical stimulation of the stomach. After holding the catheter in this position for a definite length of time, it was rapidly passed into

17. Pfaundler, M.: 16 *Verhandl. d. Gesellsch. f. Kinderh.*, 1899, p. 38.



the stomach and the gastric juice obtained. In almost every test of this nature we found hydrochloric acid. However, we were not able to establish a direct relationship between the length of time of sucking and the quantity of gastric juice. We could not demonstrate that the amount of hydrochloric acid was regularly greater in tests of one-half hour than in those of one-quarter hour, nor could we regularly produce still larger quantities in longer tests. This may have been due to congenital differences of secretion among the various infants, which, as we have shown, exist. Therefore, although our results were not sharp and definite, we believe this method of studying this question on infants deserving of further trial.

In adults the hydrochloric acid of the gastric juice, in addition to its direct function of digestion, is regarded as playing a large part in the regulation of the patency of the pyloric sphincter, and, indirectly, in the secretion of pancreatic juice. Let us briefly consider its relationship to these two phenomena at this early period of life. It has been noted elsewhere that at birth a catheter may readily be inserted through the pylorus into the duodenum. In fact, it can be passed on the new-born with greater facility and with less force than at almost any other period of infancy. Some fifty duodenal tests, made soon after birth, for the purpose of taking cultures, or of obtaining bile or pancreatic ferments, convinced us of this fact. We can therefore state with conviction that a marked tightening of the pyloric sphincter was not associated with the chlorhydria of the new-born; that there was no parallelism between these secretory and motor gastric phenomena. To further test this observation we introduced, in several cases, 1 or 2 c.c. of 0.4 per cent. hydrochloric acid and then passed the catheter. We do not wish to enter into this subject in detail, as we shall consider it at another time in connection with pylorospasm; however, we may summarize these experiments, from the present point of view, with the statement that even following the introduction of the free acid we were able to traverse the pylorus. This accords with the view of most physiologists that hydrochloric acid does not incite closure of the pylorus while it is on the gastric side of the sphincter. This does not, however, exclude the possibility that there may be a relationship between congenital gastric hypersecretion and the development of pylorospasm or of duodenal ulcer, two conditions somewhat peculiar to infancy.

#### RELATIONSHIP OF GASTRIC AND PANCREATIC JUICES

Finally, a word should be added concerning the relationship of the gastric and the pancreatic juices. In the adult the main stimulus for pancreatic secretion is regarded as the gastric juice, indirectly through its hormone action. In the unfed new-born infant the relationship does



not seem to be so intimate. At this time of life it was at all times difficult to obtain pancreatic juice; in many instances no fluid could be obtained; in others but a fraction of a cubic centimeter. There was a striking disproportion between the large amount of gastric juice and the small quantity of secretion in the duodenum. This lack of concordance may be explained by the supposition that the hydrochloric acid remains in the stomach and does not gain access to the duodenal mucous membrane. Whether or to what extent this is true we have no means of judging. However, in many cases gastric juice entered the duodenum in the course of the passage of the duodenal catheter; in others natural or artificial gastric juice was instilled into the duodenum. Nevertheless, we failed to stimulate pancreatic secretion. In similar tests performed on somewhat older infants we produced at will by this means an increased flow of pancreatic fluid. It is evident, therefore, that at birth the pancreatic secretory mechanism is either functionally undeveloped, or needs a factor in addition to hydrochloric acid to set it in action.

#### CONCLUSIONS

New-born infants regularly secrete a considerable amount of hydrochloric acid before they are given any food. Among fifty-two infants varying in age from one-half hour to eighteen hours, only one did not have hydrochloric acid in the stomach; in all but one instance free acid was obtained.

The hydrochloric acid varies greatly in amount. Exceptionally it was found almost lacking on repeated tests (congenital hypochlorhydria or hyposecretion), or very profuse (congenital hyperchlorhydria or hypersecretion).

In almost all cases acid was obtained throughout prolonged tests, in spite of the fact that food was not given to stimulate secretion. In one instance 17 c.c. of highly acid juice was aspirated in one hour and fifty minutes. Rennin, pepsin and lipase were also obtained in the (unfed) new-born.

Prevailing physiologic views cannot account for the gastric secretion immediately after birth. It is not the result of mechanical stimulation by means of the catheter, as the juice was obtained immediately on the introduction of the tube, without an intervening latent period. It may be prenatal in origin. Nor is it clear what stimulates the continued secretion which was obtained for hours. Experiments showed that the saliva is not the exciting agent; the effect of sucking could not be determined. Comparative tests of the same infants at birth and later, during the first week of life, showed that the stimulus to gastric secretion may be greater in the new-born infant which has not been fed.

This chlorhydria of the new-born is not usually associated with increased tonicity of the pyloric sphincter, as the duodenal catheter can readily be passed through the pylorus. Even when 0.4 per cent. hydrochloric acid is instilled into the gastric cavity the catheter can be readily passed into the duodenum. However, the high acidity may at times be related to the pylorospasm or to duodenal ulcer met with in infancy.

Although gastric secretion is so marked in the new-born, duodenal and pancreatic secretion is very scanty. Nor can this secretion be readily stimulated by allowing hydrochloric acid to enter the duodenum. Evidently the mechanism of pancreatic secretion is not as easily activated in the new-born as in later infancy.

# PROGRESS IN PEDIATRICS

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## REVIEW OF THE LITERATURE ON NOSE AND THROAT WITH REFERENCE TO CHILDREN

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The lymphatic area of the nasopharynx and pharynx is an immense portal of ingress for infection. Any disease, systemic or local, involving these areas, manifests very rapidly systemic phenomena. In children these areas are particularly susceptible to infection. The digestive tract in children, on account of its incomplete development, requires the closest attention as to diet, as any slight irregularity will produce digestive disturbance, and such digestive disturbance is rapidly manifested in the lymphatic areas of the pharynx and nasopharynx, rendering these areas particularly susceptible to local infections; and in many instances of a sudden febrile condition in children, the real, underlying cause will be found in the intestinal disturbance, and treatment directed toward the removal of this cause will rapidly relieve the pharyngeal and nasopharyngeal symptoms.

In the so-called infectious diseases of children — measles, diphtheria, scarlet fever, etc. — these lymphatic areas are of the greatest importance from the standpoint of diagnosis and treatment. In other words, the lymphatic area of the pharynx — the tonsillar ring and the nasopharynx — is a great barometer to the system. Journalistic literature is replete with reports illustrating just such conditions, and the general practitioner and the specialist should pay particular attention to these areas in diseases of the very young.

### CARE OF NOSE AND THROAT IN CHILDREN

Harold Hays<sup>1</sup> states that the most common portal of entry of infection is through the mouth; the nose deserves second place. (a) Whether the tonsils exercise some individual function such as that of an internal secretion is questioned. During the first two years the tonsils should not be removed unless they cause some definite symptoms, such as impairment of breathing, attacks of tonsillitis, or tendency towards suppuration of glands of the neck. If it is necessary to remove tonsils, enucleation is the only operation permissible. (b) Children with high-arched palate and narrow nasal orifices should be referred to the orthodontist. (c)

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1. Hays, Harold: *Am. Jour. Obstr.*, November, 1912.

Adenoids, if present, should be removed. (d) The sinuses of the nose are more open to infection than one usually supposes. A so-called cold in the head, discharging pus, excoriations around nostrils, red swollen mucous membrane, are the usual symptoms. For this class of cases Hays recommends the use of a spray in older children and a medicine dropper for younger children, using liquid petrolatum (albolene) having a few drops of 1-10,000 epinephrin solution, or if using boric acid or an alkaline solution, it should be followed by an oily solution.

#### THE TONSILS IN CHILDHOOD

J. Gordon Wilson<sup>2</sup> draws some very helpful conclusions bearing on tonsillar disease, especially relevant to the pediatrician, which he has made from anatomic and physiologic observations. He says:

The ease with which the palatine tonsil is observed and the association which it has in the minds of many with all kinds of diseases, lead often to a self-satisfying yet inaccurate diagnosis. Forgetful of its intimate relation to pathologic processes in the nose and naso pharynx, and of its frequent association with systemic disturbances, we too readily diagnose as a primary pathologic condition what is in reality a secondary pathological result. In a tonsillar enlargement we often erroneously see an active pathologic process instead of a hyperfunctioning organ.

His conclusions are as follows:

1. Since comparative anatomy shows that in all cases a communication with the pharynx has been preserved, it would appear that intimate relationship with the pharynx is a necessity to tonsillar activity.

2. The tonsillar activity is to be regarded as most active during developmental life. There is no evidence that in man it should be regarded as a recessive organ.

3. The tonsil cannot be regarded as merely a lymphatic node. Though it presents microscopically adenoid tissue, yet its developmental history and its physiologic activity at least make us pause before drawing such a conclusion. It is just this presumption that has led many to a hasty and unnecessary enucleation. The statement some have made that since the tonsil is only a lymphatic gland, its activity can readily be replaced by other lymphatic structures, is of very doubtful merit, even so far as lymph-nodes are concerned, and erroneous so far as the tonsil in the child is concerned.

4. We have every reason to believe that the tonsil plays an important rôle in the complex changes which occur at the upper end of the alimentary tract. The argument that no one has seen any local or systemic deficiency following removal of tonsils in childhood is not satisfactory, since we have not sufficient observations based on complete enucleations.

From these anatomic and physiologic considerations, the author distinguished in the life-history of the tonsil two distinct periods:

- (a) Before puberty — period of functional activity.

- (b) After puberty — when it persists chiefly as an aggregate of lymph-nodules which tend to atrophy.

The influence which these observations have on the author's views in regard to tonsillar diseases, and their treatment, is:

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2. Wilson, J. Gordon: *AM. JOUR. DIS. CHILD.*, 1912, iii, 277.



In the child it should be conservative, so far as possible, and the younger the child the more conservative; in adults, let it be radical whenever necessary.

He then goes on to apply these deductions to some varieties of tonsillar disease. Throughout the paper the author takes the part of the often massacred tonsil, and pleads for it a more unprejudiced study than has heretofore been given it.

#### RELATION OF ADENOIDS AND RECURRENT VOMITING

J. P. Sedgwick<sup>3</sup> reviews the theories advanced concerning the etiology of recurrent or periodic vomiting and reports a series of twenty-two cases, of which twenty patients had adenoids or enlarged tonsils. Most of them had fever before or during the attack. The posterior cervical lymph-nodes were enlarged. A very common prodrome of the attack was sore throat or nasal discharge. One "had bleeding nose at the time of the attacks." Geographical tongue and asthma were noted. He also shows by the detailed report of eight cases that these attacks were either improved or entirely relieved since the removal of the adenoids.

#### RECURRING ADENOIDS IN CHILDREN

L. Fischer<sup>4</sup> points out that a recurrence of adenoid vegetation may be due to lack of proper aseptic precautions at the time of operation. If, however, these were taken we should look for syphilis as the underlying factor. In such cases the Wassermann reaction will be found of great diagnostic value.

T. Guthrie<sup>5</sup> feels that true recurrence of adenoid tissue seldom occurs, if the removal was complete and the surface was left smooth and free from any palpable fragments. When the child is under 4 years the chances of recurrence are much greater; between 4 and 7 the risk is less, and after 7 years almost *nil*. Recurrence is favored by an attack, within a short time of the operation, of one of the specific fevers (measles or whooping-cough); by congenital syphilis, or by the presence of untreated anterior nasal obstruction, especially hypertrophied inferior turbinates.

#### ACUTE RHINITIS IN THE NEW-BORN

Rabasa<sup>6</sup> points out that coryza is not only a troublesome, but also a serious affection in childhood, because the nasal obstruction interferes considerably with feeding and also causes complications in the ears (otitis) or larynx (glottic spasms). The origin and therapy are discussed. Rabasa prefers the suction treatment by means of the Escat apparatus or an ointment of resorcin and aristol to other methods.

3. Sedgwick, J. P.: AM. JOUR. DIS. CHILD., 1912, iii, 318.

4. Fischer, L.: Jour. Am. Med. Assn., Jan. 13, 1912, p. 106.

5. Guthrie, T.: Lancet, London, April 20, 1912.

6. Rabasa: Bol. med., April, 1912.

## A FAMILY WITH MEMBRANOUS DISCHARGE FROM NOSE

A. M. Gossage<sup>7</sup> says that fibrinous rhinitis is not uncommon in children, and is associated with fibrinous or membranous exudation. It generally persists for six to eight weeks. A bacillus very closely simulating the Klebs-Loeffler is most generally found.

Baumgarten describes a case of a baby who had crust formation in the nose from birth, which, when removed, would reform in three to four days. Iodoglycerin was used to douche the nose, after which crusts did not reform. There was an odor from the nose at 3 years, and ozena at 4 years of age. Mother had ozena, but other children normal.

Gossage came across a family with several members having membranous discharge throughout life. No signs of ozena. Complete fibrinous casts were obtained from father and two children, reforming every twelve hours. Pathologically, they showed polymorphonuclear cells in fibrinous network. There were no bacilli, diplococci or diplobacilli present. History shows four generations affected.

PATHS OF RHEUMATIC INFECTION AND THEIR PROTECTION  
IN CHILDREN

J. R. Mackenzie<sup>8</sup> says that the rheumatic infection may be localized in the throat, bronchial tubes or unhealthy intestinal tract; the micrococcus makes inroads if the physical resistance, the protective properties of the local tissue or the defensive agencies of the blood are subnormal. In a child of a rheumatic family, congestion of the pharynx, palate and fauces should always receive immediate attention; salicylic acid preparations, with sodium bicarbonate, sodium salicylate, potassium chlorate and aperients are effective. The hygiene of the mouth should also receive careful attention.

PERMANENT WHEEZING IN A YOUNG INFANT DUE TO SIMPLE  
TRACHEOBRONCHIAL ADENOPATHY

Halpire and Carpentier<sup>9</sup> report a case in which, since the age of 3 months until death following bronchopneumonia complicating measles, the child had a persistent wheezing due, it was thought, to hypertrophy of the thymus. The mother had presented a similar condition, when young, which gradually disappeared. Neither during life nor at autopsy could any tuberculous lesions be found, but a very pronounced intertracheobronchial adenopathy involving the tenth pair and the recurrent nerve. Persistent wheezing is exceptional and usually ends fatally in infants.

7. Gossage, A. M.: *Brit. Jour. Child. Dis.*, April, 1912, p. 157.

8. Mackenzie, J. R.: *Brit. Med. Jour.*, June 1, 1912, p. 1232.

9. Halpire and Carpentier: *Rev. méd. de Normandie*, Feb. 25, 1912.

CONDITION OF NOSE, THROAT AND EAR AS FACTOR IN  
EXCEPTIONAL DEVELOPMENT

O. Glogau<sup>10</sup> bases his conclusions on a study of exceptional children in Herbart Hall. He found nasal obstruction with or without adenoids and tonsils present in both the advanced and the backward child. On the other hand, defects in the sound-conducting and sound-perceiving apparatus resulting in decreased hearing-power was only found in the backward children; in fact, the advanced type showed over-acute audition. This latter fact Glogau advances as a possible explanation of the musical prodigy. The function of the static apparatus of the labyrinth was found to be markedly impaired in the backward child, while in the exceptionally bright child an over-irritability was noted.

A BRIEF REPORT OF AN EPIDEMIC OF SORE THROAT WITH INVOLVEMENT  
OF THE CERVICAL LYMPH-NODES

John Ruhräh<sup>11</sup> reports that in 600 odd cases of epidemic sore throat there were twenty-eight fatalities. Complications were severe and numerous; 30 to 40 per cent. had otitis media, nearly as large a number had irregular swellings of the neck over the epiglottis, base of tongue, etc., suppuration being unusual. Edema of the eyes was common, as was bronchitis and pneumonia as a complication; also gastro-intestinal disturbances; three cases of erysipelas and involvement of tissues around joints.

A diplococcus, often in pure culture, was isolated from a number of patients; had a distinct capsule, being Gram-positive. Nearly 80 per cent. of the children were using milk from one dairy, which had temporarily discontinued its customary pasteurizing of milk, the weather at this time being extremely cold.

CONGENITAL EDEMATOUS PROLAPSE OF THE NASAL MUCOUS MEMBRANE  
IN THE NEW-BORN

N. Calamida<sup>12</sup> (Milan) reports the following two cases: Case 1. In a baby of 20 days a polypus projects from the right nostril. It is of the size of a small nut and of pinkish color. Breathing is interfered with. The growth is removed by the cold wire snare. Microscopic examination reveals the presence of juvenile connective tissue impregnated with serum; there is also present a small cell infiltration limited to the sub-epithelial layer.

Case 2. The left nostril of a baby of 24 days is obstructed by a polypus similar to the one described above. By instillation of menthol,

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10. Glogau, O.: *Am. Jour. Obst.*, January, 1912.

11. Ruhräh, John: *AM. JOUR. DIS. CHILD.*, November, 1912.

12. Calamida, N.: *Arch. Internat. de Laryngol.*, 1912, xxxiv, 61.

cocain and epinephrin the growth soon shrunk and nasal breathing was restored. The author considers this condition to be a congenital edematous prolapse of the nasal mucous membrane.

REMOVAL OF ADENOIDS AS PREVENTIVE MEASURE AFTER EXPOSURE TO  
MEASLES

J. B. Greene,<sup>13</sup> appreciating the great danger of a suppurating ear complicating measles in the presence of a large adenoid, believes that in such adenoid cases surgical intervention becomes conservative treatment after exposure to measles. He quotes a case in support of his contention.

A CASE OF FATAL HEMORRHAGE FROM THE THROAT

J. D. Rolleston<sup>14</sup> reports the case of a girl, aged 6 years, who was admitted to the hospital October 22, certified to be suffering from diphtheria. She had had measles five weeks previously, since which time her voice had been husky. October 20 she complained of sore throat, and October 22 she had a croupy cough and her neck glands became swollen.

Condition on admission: Deposit on both tonsils and uvula, slight nasal discharge, voice husky, stridor, croupy cough and dysphagia. Temperature 100 F. Sixteen thousand units of antitoxin given.

October 22. Deposit clearing away, leaving marked ulceration of tonsils and uvula. No fetor. No Vincent's organisms in throat smear. Temperature 100.2 to 100 F.

October 25. Sudden and profuse hemorrhage from throat, cyanosis and death within five minutes. No diphtheria bacilli, but only cocci were found in three successive cultures from throat and one from nose.

Necropsy, October 26. Abscess cavities in both tonsils; ulceration of uvula, soft palate, epiglottis, frenum epiglottidis, vallecule and ary-epiglottidean folds. Deep ulceration of laryngeal portion of pharynx exposing muscular tissue. Three small superficial ulcers above right vocal cord. The exact site of the bleeding vessel was not determined, but there was no evidence of erosion of external carotid, internal carotid or internal jugular, nor any glandular abscess.

Walter B. Maurice<sup>15</sup> reports a similar case, the patient being a boy, aged 6 years, sent to the hospital with supposed mastoid abscess. On examination he was found to have no mastoid trouble, but a much enlarged tonsil on the left side and free hemorrhage from the left ear. He had a fairly high temperature. The blood coming from the ear was bright and not mixed with pus. The following day marked respiratory obstruction was present and the tonsil was opened by the introduction of

13. Greene, J. B.: *Med. Rec.*, New York, 1912, ii, 388.

14. Rolleston, J. D.: *Brit. Jour. Child. Dis.*, February, 1913.

15. Maurice, Walter B.: *Brit. Jour. Child. Dis.*, May, 1913.



a pair of sinus forceps. No pus was evacuated, but the condition improved. For the next day or two the child seemed much better, but more hemorrhage occurred from the ear and temperature remained high. On the third day, while playing he suddenly gushed up a quantity of blood from the throat and dropped back, instantly dead. No post mortem was permitted, but from the great rapidity of death, the source of the hemorrhage was believed to be the carotid. The strangest feature was the hemorrhage from the meatus beforehand. The condition was obviously a septic one from the start, but there was no history or evidence of scarlet fever.

#### PERTUSSIS: THE HISTOLOGICAL LESION IN THE RESPIRATORY TRACT

F. B. Mallory and A. A. Hornor<sup>16</sup> conclude, from a microscopic study of the trachea and lungs from three patients who died of whooping-cough, that this disease is due to a minute bacillus which occurs in large numbers between the cilia of the epithelial cells lining the trachea and bronchi and possibly also the nose. The location of the organism is apparently characteristic for the disease. Its action seems to be largely mechanical. It interferes by its presence with the normal movements of the cilia and possibly leads to their destruction.

The mechanical interference with the action of the cilia, and possibly their destruction, prevent the normal removal of secretion. The bacilli and the secretion produce a continuous irritation which results in coughing, and usually also in the characteristic spasm known as whooping.

Believing that the bacillus found in the lesions was in all probability identical with the organism discovered and described by Bordet and Gengou, they subsequently<sup>17</sup> carried out experiments on animals which proved that the organism corresponded in every way with the Bordet-Gengou bacillus.

The failure up to the present time to observe the bacillus of whooping-cough in its peculiar and characteristic location in the respiratory tract is probably due to its small size and to its staining but faintly by ordinary methods.

The reason the Bordet-Gengou bacillus has not been unqualifiedly accepted as the cause of whooping-cough is largely due to its presence having been demonstrated only in connection with the disease, not in connection with any evident lesion. It might have been a secondary invader like the streptococcus in scarlet fever.

Mallory and Hornor have demonstrated the primary essential lesion of the disease and the characteristic relation of the causal agent to it. In addition, they have been able, with sputum and with pure cultures of a micro-organism corresponding in every way with the Bordet-Gengou

16. Jour. Med. Research, xxvii, No. 2, Nov., 1912, p. 115.

17. Jour. Med. Research, xxvii, No. 4, March, 1913, p. 391.

bacillus, to produce the same characteristic lesion in young animals and in four instances (one puppy and three young rabbits) to obtain the organism again in pure culture. Moreover, they have produced the same lesion in the nares, trachea and bronchi of a young rabbit after infecting it through the nares with a subculture of the bacillus obtained originally from Bordet, and were able to grow the micro-organism again in pure culture. They have, therefore, supplied the steps which have heretofore been lacking, according to Koch's laws, for the complete demonstration that the Bordet-Gengou bacillus is the cause of whooping-cough. This result should encourage further investigation in search for a vaccine or antitoxin which may be of use in the treatment of the disease. The diminution in numbers and final disappearance of micro-organisms under ordinary conditions in the course of comparatively few weeks strongly suggests that conditions for growth become unfavorable, probably owing to the development of some antibody.

#### VACCINE THERAPY OF WHOOPING-COUGH

C. Nicolle and A. Conor<sup>18</sup> recently presented before the Academie des Sciences, Paris, the results of their attempts at vaccination of whooping-cough by inoculation of living cultures of Bordet's bacteria, which they used during the epidemic which raged in Tunis last spring. These cultures on agar-potato-blood, made into an emulsion in physiologic salt solution, were kept at 46 C. (114.6 F.) for thirty minutes, which does not affect their vitality, then repeatedly washed and centrifuged so as finally to obtain a perfectly homogeneous emulsion of bacteria, isolated and deprived of all foreign substances. For use in vaccination, each drop of the emulsion (representing about 400 million bacteria) is diluted with 2 c.c. of physiologic salt solution. Because of the difficulty of intravenous inoculation of very young children, Nicolle and Conor inject it under the skin of the thigh, from 1 to 5 drops of emulsion each time. They have observed no general or local reaction. Of 122 children treated thus, 18 have not been seen after the first inoculation. Of the remaining 104, there have been 37 cures (complete cessation of cough), or 35.37 per cent.; 40, or 38.46 per cent., improved (notable diminution of cough) and 27, or 25.96 per cent., remained stationary. In the cases of cure, improvement became manifest very rapidly, generally on the first or the second inoculation. The nightly coughing spells diminished in intensity and number. Out of the 37 cures, 29, or 78.38 per cent., occurred after from two to five inoculations; that is, in from three to twelve days. In view of the often discouraging duration of whooping-cough, the results obtained by Nicolle and Conor are distinctly encouraging.

1517 Walnut Street.

18. Jour. Amer. Med. Asso., lxi, No. 3, July 19, 1913, p. 209.

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# American Journal of Diseases of Children

Vol. 6

NOVEMBER, 1913

No. 5

## HEAT AND SUMMER DIARRHEA \*

JOHN ZAHORSKY, M.D.

ST. LOUIS, MO.

The theory that the extreme elevation of the temperature during July, August and September is the direct cause of summer diarrhea was very popular with the early American physicians. Booker<sup>1</sup> has given us an interesting history of the subject. Diarrhea in infancy as a summer disease was not recognized in Europe until recent times, but was accurately described by Benjamin Rush of Philadelphia in 1777. To this physician is also credited the theory that heat is the principal factor in the causation of the disease, but a careful reading of his article shows that he was inclined to view the disease as a modification of malaria. It was really Dr. E. Hornell of Philadelphia in 1823 who first clearly expressed the direct connection between heat and cholera infantum. He wrote:

Whatever consideration attaches to irregularities in diet, inattention to cleanliness, difficulty of dentition, etc., I am disposed to consider the violent heats of the summer in conjunction with sudden aerial vicissitudes, or with exposure to a moist and vitiated atmosphere, as the most usual exciting cause of the complaint.

Another writer, J. P. Harrison of Louisville, Ky., in 1828, also considered atmospheric heat to be the general predisposing or remote cause of the disease and improper diet the most important exciting cause.

Dr. J. E. Cooke and others, at this period, denied the direct influence of atmospheric heat. Cooke declared that "there is evidently something more than heat necessary to the production of the disease."

Dr. Nathaniel Potter, 1833, also emphasized the importance of the high temperature and rejected marsh effluvia from the list of causative agencies. Eberle,<sup>2</sup> 1834, in discussing the various varieties and causes of diarrhea makes this statement: "There can be no doubt that high atmospheric temperature, by its direct influence on the system, is capable of giving rise to diarrheal affections." Eberle's teaching was dominant for fully fifty years in America, but additional factors were proposed by

\* Read before the St. Louis Medical Society, May 31, 1913.

1. Booker: Arch. Pediat., 1901, xviii, 481.

2. Eberle: Diseases of Children, 1833, p. 215.

many writers. Meigs became the chief supporter of the theory of dentition and his authority had great weight with the general practitioner, and this teaching has not entirely died out even at present. Another prominent man who gave heat a prominent place in the etiology of summer complaint was Condie, who insisted, however, that the application of cold to the surface of the body or a sudden transition from a close and heated to a chilly and humid atmosphere will in many cases give rise to a diarrhea.

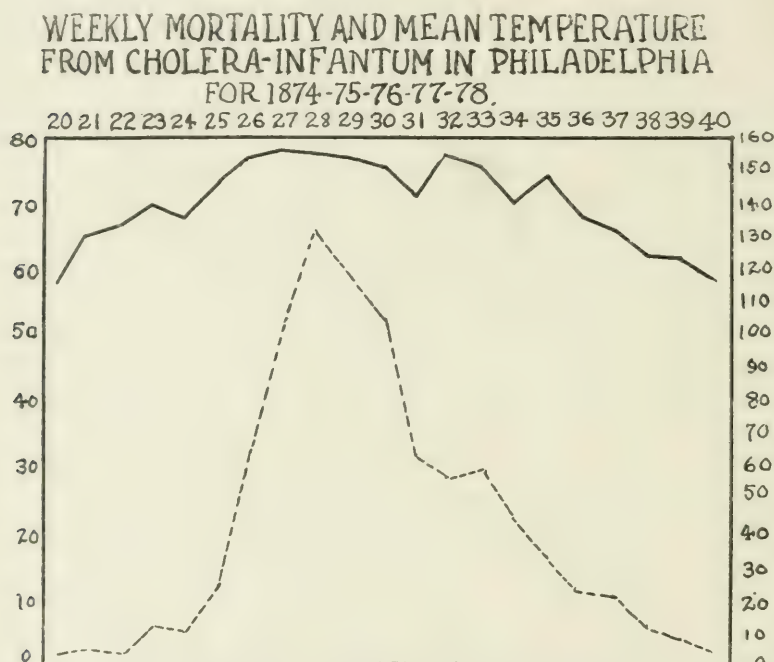


Fig. 1.—Drawn from Miller's statistics. No parallelism between the lower (mortality) curve and the upper (heat) curve.

The subject of heat and diarrhea received considerable discussion after the publication of an article by T. Clarke Miller,<sup>3</sup> who asserted:

The condition under which cholera infantum appears, and the only condition essential to its development, is a continued high temperature day and night, and mean thermometer above 75 degrees with small daily range. This high and slightly varying temperature continuing from six to ten days will invariably, in our climate, bring cholera infantum, and the longer this condition of things continues the more numerous and intractable the cases become.

He collected the statistics of the mortality from diarrheal diseases from Philadelphia, New York, Boston, Baltimore, Cincinnati and Chicago, and gives the weekly mean temperature and the number of

3. Miller: *Am. Jour. Obst.*, 1879, xii, 236.



deaths during the summer months. While there are numerous exceptions, the figures substantiate his theory to a remarkable degree (Figs. 1 and 2).

This position was vigorously combated by Woodbury,<sup>4</sup> who ventures "to differ *in toto* with him and other writers who adhere to the view that the degree of heat *per se* is sufficient to cause the disease." To quote further:

We oppose it the more firmly because this teaching, which has now become fashionable, leads to erroneous therapeutic deductions; we are permitted to infer that a case resembles one of heat-stroke or thermic fever and, therefore, is to be treated by the extraction of bodily heat. Think of treating an adult with cholera morbus in this way. It is also leading us in the wrong direction for prophylaxis, for it teaches that if the baby can be kept cool it is safe.

Average weekly mortality & mean temperature  
from diarrhea in Boston under 5 yrs. for 1874, 75, 76, 77.  
25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42



Fig. 2.—Drawn from Miller's statistics. Marked parallelism in the decline, but not the ascent of the curve.

He disparages the prophylactic measure issued by the New York Board of Health, "Wash your well children in cold water twice a day and oftener in the hot season." Furthermore, he insists that we should search deeper for the cause of summer diarrhea.

His principal objection to the heat theory may be summarized as follows: That children resist heat better than adults; that infants are often kept at a temperature of 75 degrees in the homes during the winter

4. Woodbury: Med. and Surg. Reporter, 1879, xli, 177.

for weeks; that the geographical distribution is different from what would be expected if heat was the chief cause, and that pathological considerations show that disease corresponds closely to cholera morbus in the adult.

In a reply to this article, Miller<sup>5</sup> emphasized his previous position, and points out some weaknesses in Dr. Woodbury's argument.

Atkinson,<sup>6</sup> in discussing the various causative agencies, filth, heat and improper food, is forced to the conclusion that there must be other etiological factors. Bigelow and others about this time were insisting



Fig. 3.—After Seibert. Dotted line, mean temperature; solid line, mortality. New York.

that cholera infantum must be clinically separated from enterocolitis and simple diarrhea. The older writers seem to have used these terms interchangeably, and much of the discussion has arisen from different writers studying the effects of heat on particular clinical forms. Here, however, we are concerned with all the diarrheal diseases of infants.

5. Miller: Med. and Surg. Reporter, 1879, xli, 282.

6. Atkinson: Med. and Surg. Reporter, 1880, xliii, 50.

An important study of the subject was made by Seibert<sup>7</sup> of New York. He gathered all the cases of acute gastro-intestinal catarrh in children under 5 years of age treated at the German Dispensary during a period of ten years, also the mortality of diarrheal diseases in New York for the same period and arranged the cases according to the different months. Curves of the number of cases and the average monthly temperature gave two figures which are well known (Figs 3 and 4).

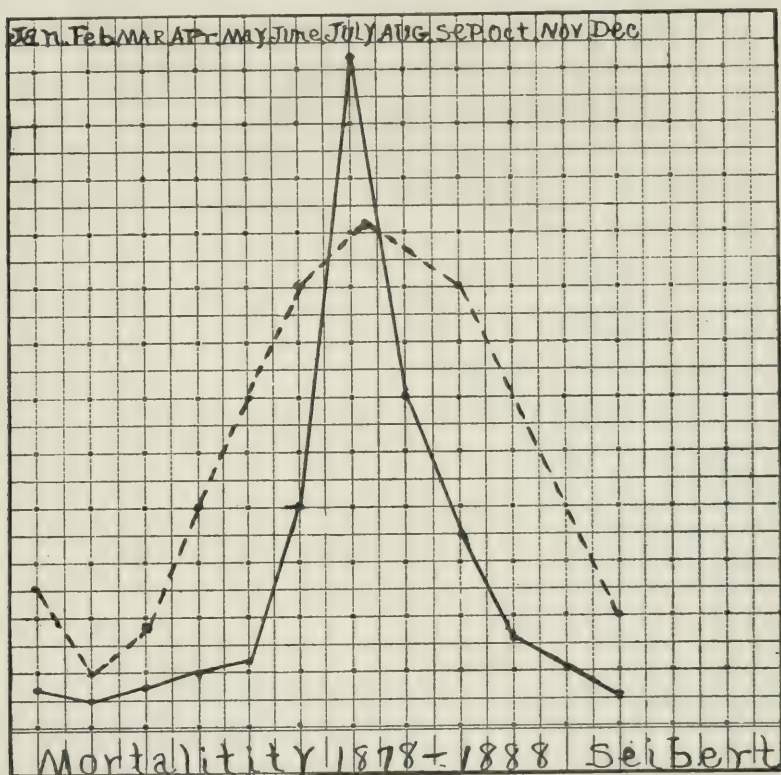


Fig. 4.—After Seibert. Dotted line, mean temperature; solid line, mortality. New York.

Seibert pointed out that the disease is present throughout the year, not frequently in January and February, but it does appear even in cold weather. The morbidity and temperature lines run in the same direction, but are not parallel. The greatest difference exists in morbidity between June and July, while the difference of temperature is not nearly so great as between May and June. He draws the remarkable conclusion from this study that the proportion of deaths is exactly the same in winter as

7. Seibert: Med. Rec., New York, 1888, xxxiii, 24.

in summer, during the hottest as well as during the coldest weather. He finds numerous discrepancies between the degree of heat and the morbidity and mortality. "One July may be hot and have many cases and the next may be exactly as warm and only have half the cases." The variability of the disease in different months and years does not correspond to the degree of heat. Several forcible examples are given, one of which may be quoted:

But the most striking example is July, 1884, during which time the temperature never reached 90 degrees, passed 85 degrees but on three days, and altogether reached 80 degrees but on eight days, showing a remarkably cool summer month, and yet we have 266 cases of summer-complaint; while the following August had sixteen days where the temperature reached 80 degrees, four

MEAN TEMPERATURE AND MORTALITY  
IN WASHINGTON FOR 1910.  
JAN. FEB. MAR. APR. MAY JUN. JUL. AUG. SEP. OCT. NOV. DEC.

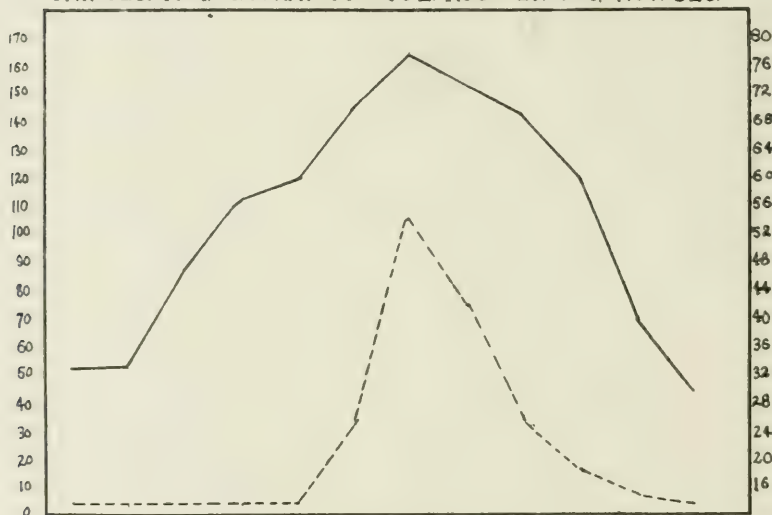


Fig. 5.—Solid line, mean temperature; broken line, mortality.

days with 85 degrees, and one with 90 degrees, and yet the number of cases is but 156, one-third less than in the preceding cooler July. I might keep on for hours and give you any quantity of evidence that very high temperatures do not favor the production of cholera infantum more than medium warm weather.

His conclusions are worthy of repetition:

1. Hot weather (either dry or moist) is not necessary for the epidemic appearance of summer complaint.
2. Warm weather (either dry or moist) showing minimum daily temperatures of not less than 60 F. brings on the epidemic appearance of cholera infantum invariably in every year, irrespective of the height of the maximal daily temperature, as in the latter part of June in every year.
3. Summer complaint loses its epidemic character as soon as the minimal daily temperature remains below 60 F., as in the latter part of October of nearly every year.



4. Therefore, this disease cannot be brought about by the direct working of high temperatures on the infantile body, but must have other causes.

The other causes, of course, are bacterial decomposition of milk and infections, the theory which had gained ground about this time. Dr. Miller<sup>8</sup> replied to this article without, however, offering any additional evidence.

American physicians generally adopted the conclusions of Seibert, and an earnest search for the other causes has resulted in the large and important work on the bacteriology of the summer diarrheas familiar to all. The work of Holt on the pathological anatomy and Booker on the

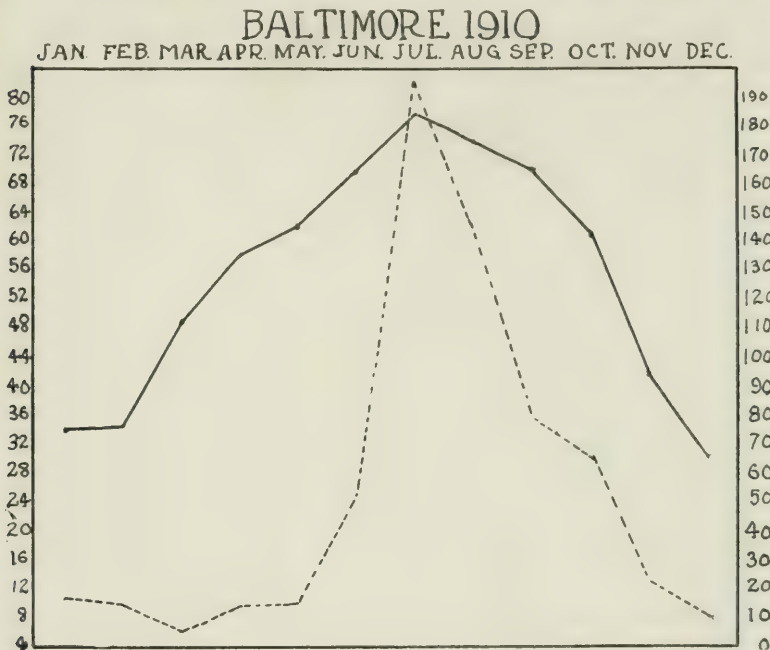


Fig. 6.—Deaths in Baltimore, 1910. Heat and mortality curves not parallel.

bacteriology of ileocolitis, strongly corroborated the earlier theories that virulent bacteria are the chief sources of the graver acute intestinal diseases. The position at that time was clearly stated by Holt:<sup>9</sup>

The chief exciting cause is something to the development of which two things have a fixed and constant relation, viz., a certain degree of atmospheric heat and the practice of artificial feeding. Both of these conditions are necessary. We believe the chief causative factor to be bacteria, and that these act in most cases by inducing changes in the food.

While we have learned in recent years that the ordinary saprophytic decomposition of milk is usually harmless, American physicians even

8. Miller: *Med. Rec.*, New York, 1888, xxxiv, 59.

9. Holt: *Keating's Cyclopedia Dis. Child.*, 1890, iii, 70.

to-day still cling to the position that certain kinds of bacteria and their products induce the most important pathologic changes in summer diarrhea. While the agency of heat is generally admitted in directly lowering the digestive and metabolic activity of the infantile organism, it is denied that the excessive heat alone without the bacterial or toxic factors would appreciably raise the ordinary morbidity of digestive and nutritive disorders in infants. We thought the question of heat had been answered, and while the bacteriology and toxicology were still unsettled we waited patiently for the difficult problem to be solved. The discovery of the different types of the dysentery bacillus and their wide distribution certainly promised to clarify the mooted question. We had already recognized from Booker's studies that a great variety of bacteria may be etiologically related to the disease. The study of the colon and dysentery

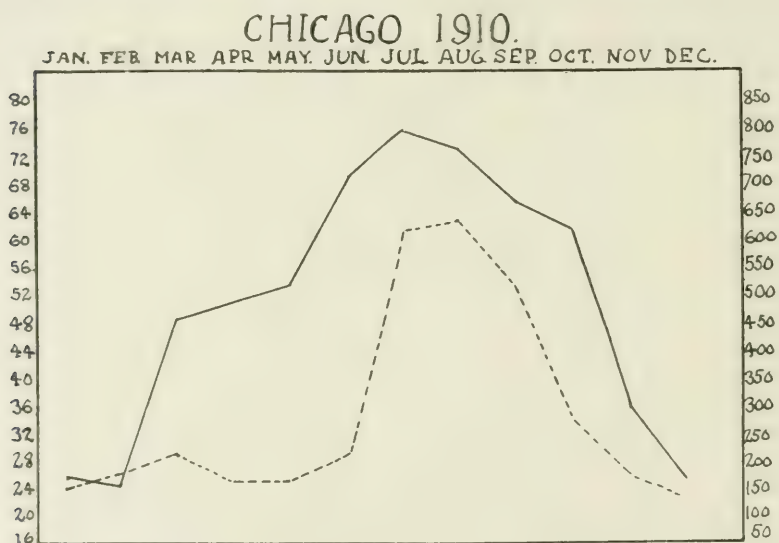


Fig. 7.—Deaths in Chicago, 1910. Note the absence of the sharp peak in the lower (mortality) curve.

group, the streptococcus group and the group classified under the liquefying bacteria, their pathogenic and toxicogenic powers, and the susceptibility and immunity of the infant offered an enormous field, and, as mentioned, we believed that we were approaching the solution of the intricate problem.

It seems, however, that the original controversy is open again, and what we had dismissed twenty years ago is brought forth in splendid attire and paraded as the long-sought causative agent. We are asked again to destroy the bogey of summer diarrhea by keeping the babies cool, and we expect our milk stations to close up and in their place conferences

will teach the mothers to give the baby several cool baths daily during the hot weather to abstract the retained atmospheric heat.

This view began with the teachings of Finkelstein, who all but discarded enteric infections from the nosology of infantile diseases. It was Rietschel,<sup>10</sup> however, who in a splendid monograph vigorously defends the old view that summer diarrhea depends almost entirely on the excessive heat of summer. In another article<sup>11</sup> he reiterates his former conclusions with increased vigor and offers additional evidence. His principal conclusions briefly stated are:

1. The summer mortality of infants is brought about by all the detrimental agencies which produce the general infant mortality, to which is added another injurious factor — the heat.

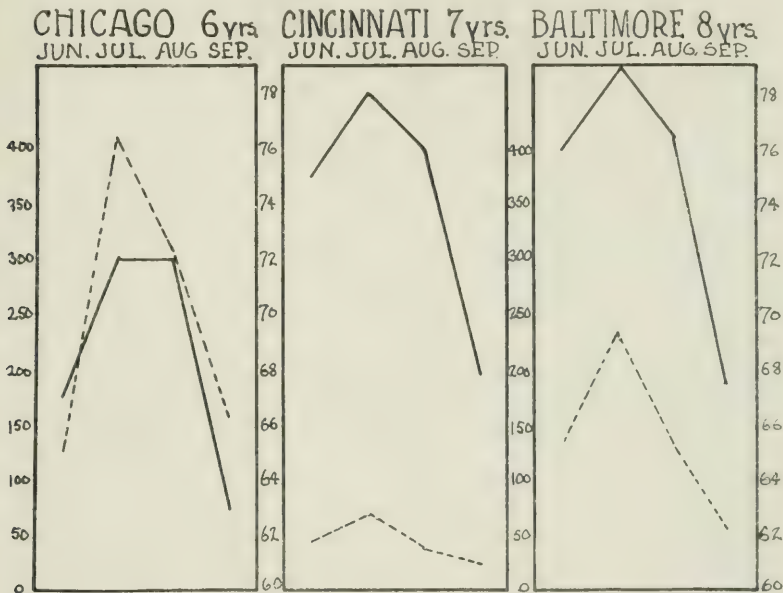


Fig. 8.—Drawn from Miller's statistics. This figure again shows that the heat and mortality curves do not correspond and vary in different cities.

2. The summer heat affects the infants through the high temperature of the living rooms, and the homes of the proletariat may be very hot even in a cool summer. The real danger of the heat to the infant lies in the rooms of the houses.

3. The action of the heat is a direct injury to the infant in producing hyperthermia, in the abstraction of water, overfeeding from the thirst, effect on the gastro-intestinal secretions and bacterial activity in the alimentary canal.

In the discussion of this subject by the *Gesellschaft für Kinderheilkunde*, 1911, several members protested against the dicta of Rietschel.

10. Rietschel: *Ergebn. d. inn. med. u. kinderh.*, 1910, vi. Complete bibliography given, page 369.

11. Rietschel: *Monatschr. f. Kinderh.*, 1910, p. 39.

but there can be no doubt that this old theory is favorably received in Germany.

What shall be our attitude on this question?

In order to assist in elucidating this subject the following study is herewith presented:

1. The mortality in different parts of the United States.

In order to ascertain what effect different climatic conditions have on the mortality of the disease the death-rate of diarrheal disease in infants under 2 years of age as given in the United States mortality statistics for the years 1907 to 1910, inclusive, were studied. For the purpose of comparison, several southern, several central and several northern cities were selected as given in Table 1.

TABLE 1.—MORTALITY FROM DIARRHEAL DISEASES IN DIFFERENT SECTIONS OF THE UNITED STATES

		Deaths in—				Death Rate per 100,000 in 1910
Cities						
Southern	Population	1907	1908	1909	1910	
Mobile .....	43,642	43	59	42	48	93.0
Jacksonville ....	38,049	48	52	37	27	46.0
Atlanta .....	107,265	151	115	122	154	98.0
New Orleans ...	318,652	463	466	345	448	131.0
Wilmington ....	21,620	45	49	49	53	205.0
Charleston .....	56,402	119	141	111	142	241.0
San Antonio ....	64,275	172	216	200	291	298.0
Central						
St. Louis .....	661,666	482	443	476	596	86.0
Philadelphia ....	1,466,408	1,886	1,835	1,791	2,336	150.0
Louisville .....	229,599	110	73	65	64	28.5
Cincinnati .....	347,123	459	301	282	328	90.0
Indianapolis ....	227,698	190	158	130	177	75.0
Northern						
Boston .....	609,175	546	724	684	678	100.0
Detroit .....	367,494	395	374	369	581	123.0
Minneapolis ....	285,676	138	255	128	240	79.0
Milwaukee .....	322,513	347	410	467	441	117.0
Buffalo .....	386,724	598	586	533	563	132.0

It will be seen from Table 1 that there is no striking difference in the death-rate of diarrheal diseases in different parts of the United States. Latitude has little influence. The common practice of sending infants to the Northern resorts or to the sea shore finds little comfort from these figures. Louisville, Ky., seems to be the ideal summer resort for babies. This singular low death-rate in Louisville is inexplicable. In reply to a personal letter, Dr. Tuley attributed this low death-rate to good milk and effective educational work among the poorer classes.

A more striking difference is found in comparing the Eastern and Western cities.

Eastern Cities Death-Rate, 1910.		Western Cities Death-Rate, 1910.	
Portland .....	73.0	Seattle .....	31.8
Baltimore .....	114.0	San Francisco .....	40.0
Atlanta .....	98.0	Los Angeles .....	24.4



## NEW ORLEANS 1910.

JAN. FEB. MAR. APR. MAY JUN. JUL. AUG. SEP. OCT. NOV. DEC.

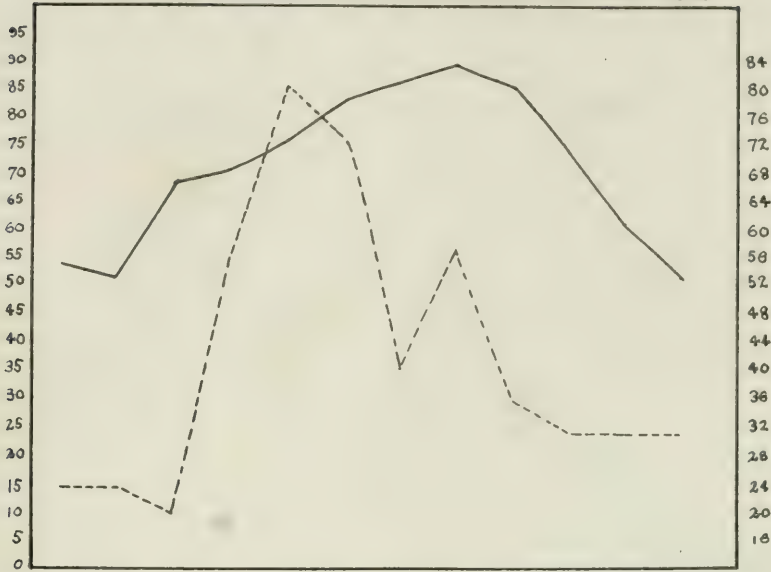


Fig. 9.—This shows the peculiar mortality curve (dotted line) shown by Southern cities. The peaks of the heat and mortality curves do not correspond, and the secondary rise in the mortality curve is characteristic.

MEAN TEMPERATURE AND MORTALITY  
IN LOS ANGELES FOR 1910.

Cases JAN. FEB. MAR. APR. MAY JUN. JULY AUG. SEP. OCT. NOV. DEC. Temp

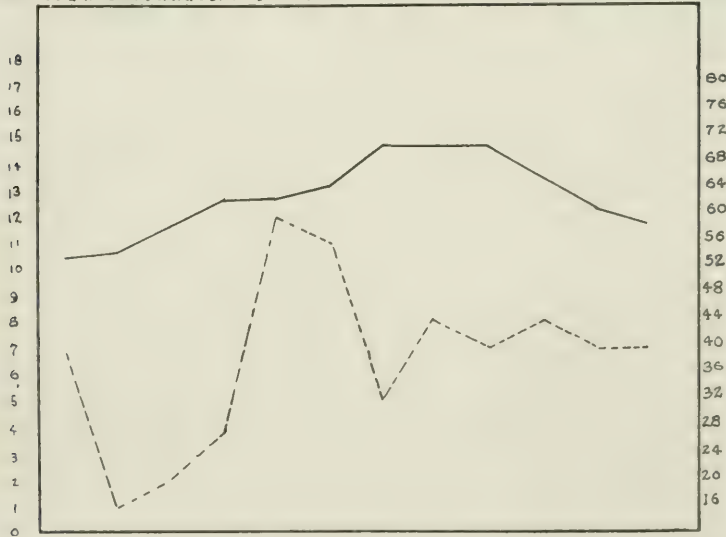


Fig. 10.—The mortality curve (dotted line) shows the peculiarity of Southern cities.

The equable temperature along the Pacific Coast certainly has a restraining influence in intestinal diseases.

It is interesting to arrange the large cities of the United States in the order of their ascending death-rates (1910).

Los Angeles .....	24.0	New York .....	123.0
Louisville .....	28.0	Detroit .....	123.0
San Francisco .....	40.0	New Orleans .....	131.0
St. Paul .....	70.0	Richmond .....	133.0
St. Louis .....	86.0	Philadelphia .....	150.0
Cincinnati .....	90.0	Chicago .....	159.0
Boston .....	100.0	Cleveland .....	169.0
Baltimore .....	114.0	Pittsburgh .....	177.0
Milwaukee .....	117.0		

It is obvious that there are other factors besides fluctuation of temperature that produce such wide variation in the deaths of infants. A comparison of the death-rate in 1910 in several states of the registration area shows no great difference north or south; the western states, however, show much lower figures.

California .....	39.0	New Jersey .....	117.0
Colorado .....	65.0	New York .....	106.0
Connecticut .....	103.0	North Carolina .....	137.0
Indiana .....	78.0	Ohio .....	84.0
Maine .....	87.0	Pennsylvania .....	144.0
Maryland .....	103.0	Rhode Island .....	153.0
Massachusetts .....	121.0	Utah .....	49.0
Michigan .....	83.0	Vermont .....	57.0
Minnesota .....	64.0	Washington .....	37.0
Montana .....	59.0	Wisconsin .....	72.0
New Hampshire .....	93.0		

Basing the death-rate of infants on the whole number of inhabitants does not give very good figures for comparison, but it is the best we can do at present.

The mortality is especially high in manufacturing cities. The following are examples:

Fall River, Mass.....	373.0	East Chicago .....	422.0
New Bedford, Mass.....	324.0	Gary, Ind. ....	404.0

The mortality in rural districts is generally less than in the large cities. Thus we find that in 1910 the death-rate from diarrheal disease in the registration area was 100.8; the cities gave the mortality as 117.8; the states, 98.7; while the rural part of the states was 77.3. In 1911 in the state of Missouri, the death-rate in St. Louis was 85 per 100,000; five adjoining counties taken at random in the central part of the state had a death-rate of 51 per 100,000 inhabitants. On the other hand, three counties in the southeastern part of the state had a death-rate of 130.

The death-rate in Missouri was 63.62 in 1911. This compares favorably with most states. The death-rate in Michigan in 1910 was 83, and

in Minnesota 64 during the same year. The rural part of Missouri is a good place to keep infants during the summer.

The relationship of the mean monthly temperature and the number of deaths in a number of cities of the United States is shown by the

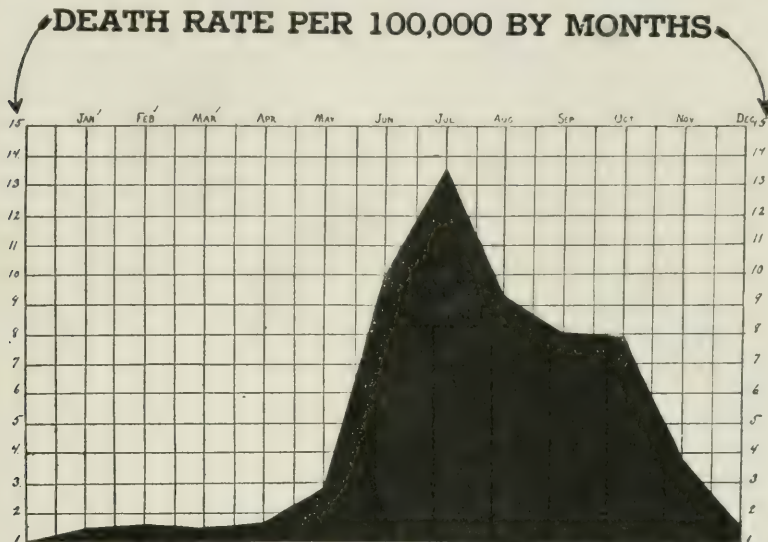


Fig. 11.—The curve of the deaths in Missouri, 1911. Note the secondary elevation in October. The last drop corresponds to the appearance of frost.

**DEATHS IN 1910 FROM DIARRHEA MONTHLY  
IN MICHIGAN, MARYLAND & WHOLE REGISTRATION AREA**

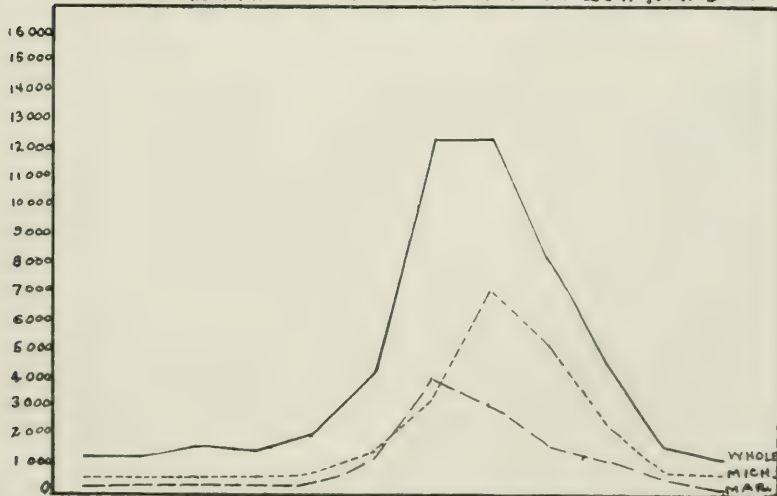


Fig. 12.—The curve of deaths over the whole registration area shows a plateau and not a peak. Note the difference in the time in the highest mortality in a Northern and Southern state.

curves (Figs. 5, 6 and 7). The curves are drawn from the temperature and death-rate in 1910. The curve of Chicago shows a peak flattened at the top. Three cities are compared in Figure 8, taken from Miller's figures.

In all northern and eastern cities there is a striking similarity. Southern cities show a different curve. The apex of the heat curve and mortality curve do not correspond, and a secondary elevation is peculiar (Figs. 9 and 10). The peak of the curve is not so sharp as that of the northern cities. A similar curve is exemplified by Missouri, 1911 (Fig. 11). A high death-rate continued until the last of October, although the temperature had fallen very much. A similar condition occurred in

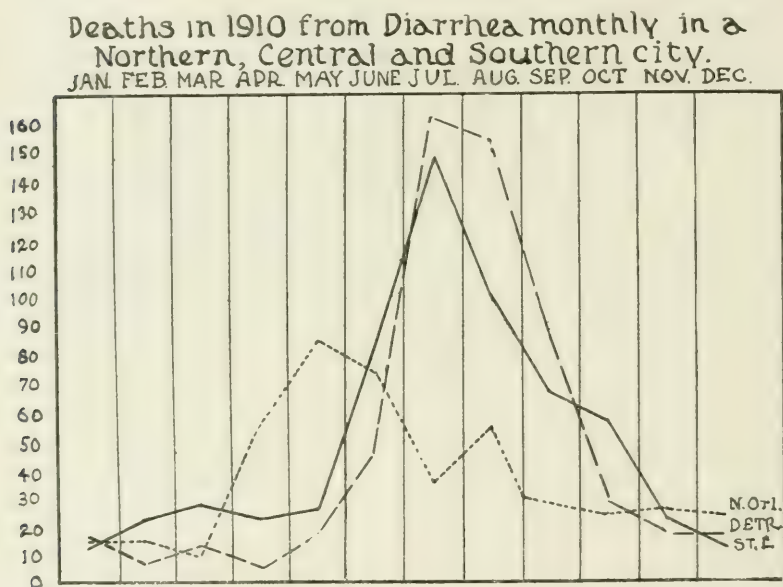


Fig. 13.—This shows the different configuration of the curves of mortality of different cities.

1912. Two states are compared with the registration area in Figure 12; three cities are drawn in Figure 13. The deaths in San Francisco show a singular curve. The mean temperature in October rose slightly above 60 F., yet there is a sharp peak (Fig. 14).

The intimate relationship of a high temperature and the morbidity and mortality is clearly shown by the classical curves of Seibert (Figs. 3 and 4).

However, his statement that the death-rate of diarrheal diseases is practically the same in winter and summer, while apparently substantiated by the configuration of the curves, is really disproved when his figures are properly analyzed. Assuming that the number of cases



treated at the German Dispensary approximately represents the morbidity of the disease, we find that the number of deaths is relatively much larger in the summer. The total number of cases seen during the four winter months was 620; the total deaths during the same period in New York were 1,476—that is, the ratio of the morbidity at the German Dispensary to the total mortality was 1 to 2.4. In July the ratio was 2,443 to 12,468, or 1 to 5. The death-rate, therefore, is at least twice as high during the summer months as in the winter months, a conclusion which corresponds to the common impression of practitioners. This difference is shown in the curves in Figure 15 in which Seibert's mortality figures are divided by two.

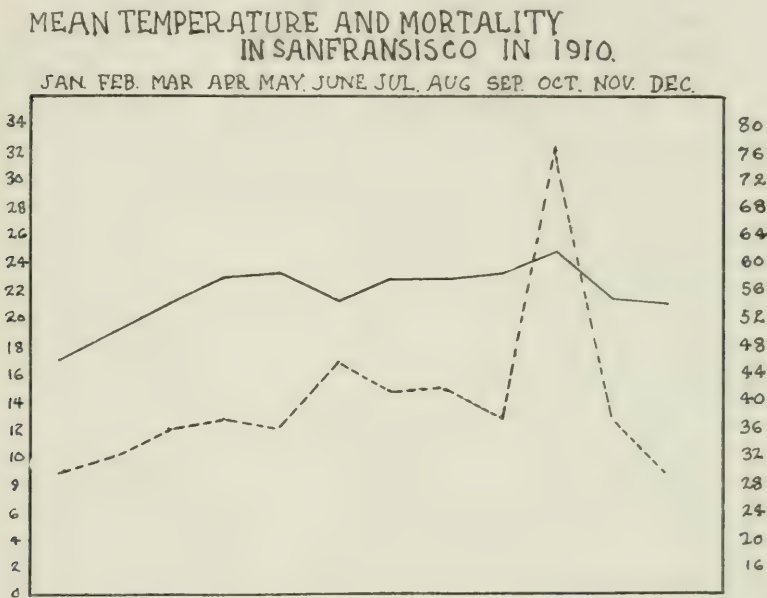


Fig. 14.—San Francisco has a singular curve of mortality; its peak (dotted line) corresponds with the peak of the mean temperature (solid line).

The relation of heat and mortality is also shown clearly by the figures published by Miller. Figures 1 and 2 are based on these, and plainly show why he was so firmly attached to the principle that heat is the essential factor. The peculiar phenomenon of a rise in mortality during the hot months is not peculiar to the United States. The rule also holds good in Europe, as has been repeatedly shown. For illustration, a chart of Budin of Paris is appended (Fig. 16).

All these studies relate to the average monthly temperature and mortality. In order to study the relationship more closely the daily number of deaths and the temperature have been compared. Copies of the curve of Finkelstein (Fig. 17) and Willan (Fig. 18) are instructive

in that they demonstrate that more deaths occur on the hot days: The curve published by the New York Milk Committee (Infant Mortality and Milk Stations, 1912), a part of which is herewith given (Fig. 19), does not agree so fully.

I have made similar curves of the daily mean temperature and deaths in St. Louis for two summers (Figs. 20, 21, 22, 23, 24 and 25).

The striking exception in August, 1911, is worth special mention. September, 1912, had some peculiarities not accounted for by the heat. Figure 26 shows deaths in St. Louis and in the state compared.

It is obvious that while many hot days show a high death-rate there are other equally as warm days in which no corresponding increase in

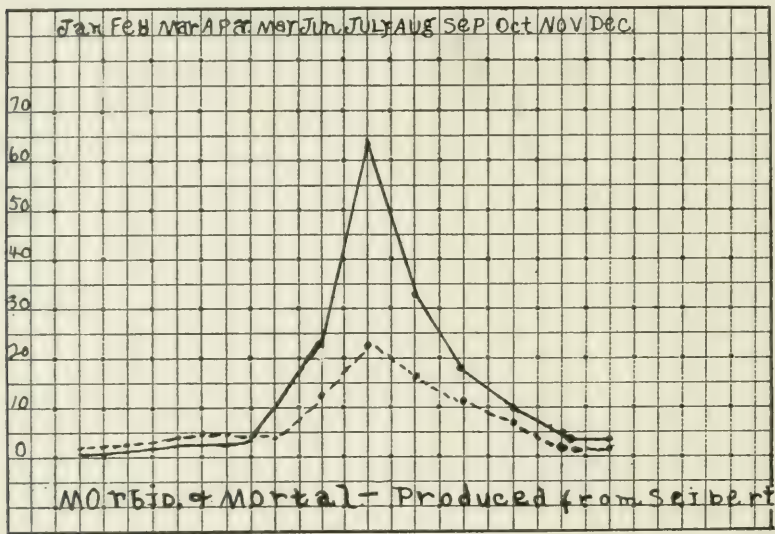


Fig. 15.—The lower curve represents the relative morbidity; the upper, the mortality. Drawn from Seibert's numbers. It will be seen that the mortality curve is much higher during the summer; that is, the death-rate is higher.

the deaths is found. Warm periods and many deaths agree closely in the beginning of the summer, but this is not true later in the season.

For the purpose of learning how long the infants who died during the days of high mortality had been sick, the mortuary records of St. Louis were studied. The death certificates give the length of the illness and from these a conclusion can be drawn whether short illnesses, such as convulsions, heat stroke, etc., make up the greater part of the death-rate.

Table 2 gives the age of the baby in months (first number) and the length of the illness in days (special number). The length of each line roughly gives a curve of the deaths. The mean temperature is affixed. The illnesses directly due to heat stroke are very few. Two cases probably

occurred on July 5. Rapid deaths from heat-stroke even in St. Louis are too few to modify the mortality curve appreciably.

In Figure 27 three months are studied to determine the onset of illness. It is perfectly clear that both morbidity and mortality in June and July are distinctly influenced by the height of the temperature. In August and September this relationship is not nearly so clear. Cool periods may be attended by a rise in mortality (Fig. 21).

TABLE 2.—DEATHS IN ST. LOUIS IN JULY, 1911.

Day	Mean Temp.	Age and Duration of Illness
1	86	6-6,* 18-2, 4-7, 9-3, 9-8, 1-10
2	88	16-37, 9-1, 1-4, 11-1, 16-3, 8-1, 9-5, $\frac{1}{2}$ -2
3	89	4-3, 3-8, 2-10, 1-4, 8-2, 1-7, 14-3
4	91	4-14, 4-18, 2-3, 21-8, 1/6-5
5	89	2-3, 2-1, 2-8, 6-1, 9-14, 8-7, 2-39, 4-12, 21-14
6	85	2-4, 4-3, 6-12, 6-2, 15-2, 9-10
7	85	27-5, 14-3
8	83	5-2, 14-2, 10-1, 5-10, 7-3, 4-2, 9-5, 4-4
9	83	13-19, 6-1, 14-2, 4-4, 12-4, 4-3, 7-30, 9-60, 20-6
10	84	4-20, 23-4, 3-21
11	86	5-5, 12-4
12	81	17-4, 6-60, 10-1
13	79	12-43, $\frac{2}{3}$ -10, 2-35
14	80	5-5, 20-5, 15-6, 4-2, $\frac{2}{3}$ -20, 2-10, 2-60, 1-1
15	82	6-14, 6-2, 7-6, 2-14, 12-2, 11-9, 12-18
16	75	9-13, 20-3
17	73	4-7, 3-4
18	72	4-13
19	73	6-10, 12-24, 8-5, 8-30, 4-34
20	76	1-9, 3-1, 8-12
21	81	9-4, 11-3, 2-4
22	79	7-7, 4-27, 10-15
23	78	16-22
24	69	7-6, 8-18
25	68	9-2, 11-10, 6-25, 5-30
26	69	10-14, 10-26, 6-11, 19-5, 7-1
27	76	18-4, 4-60, 4-20, 17-2
28	74	28-10, 9-5, 3-60, 1-2
29	75	13-9, 5-9, 10-30, 10-14, 9-30
30	76	24-4, 8-9
31	78	10-3, 5-2, 3-18, 3-20, 6-2, 2-10

\* First number, age in months; second number, length of illness in days.

Clinical experience shows that the cool weather in September and October may be accompanied by an increase in diarrhea (Fig. 25).

America is known as the country of extreme variations in temperature, and to this physical character has been ascribed the great prevalence and high mortality of diarrheal diseases. As various parts of the United States exhibit this variation in temperature in a different degree, an inquiry into the death-rate and heat variation may be instructive. Figure 28 is based on the difference in temperature of the winter months (December, January and February) and the summer months (June, July and August) in 1910 in several cities of the United States.

Observation in St. Louis has convinced me that it takes two or three days of very warm weather to heat the interior of our brick houses to the extreme temperature. When this heating is accomplished the daily temperature variation is much less in the houses, and sleep, even for adults, is difficult at night. These are trying times for infants suffering from vomiting and diarrhea. Liefman and Lindman have attempted to prove

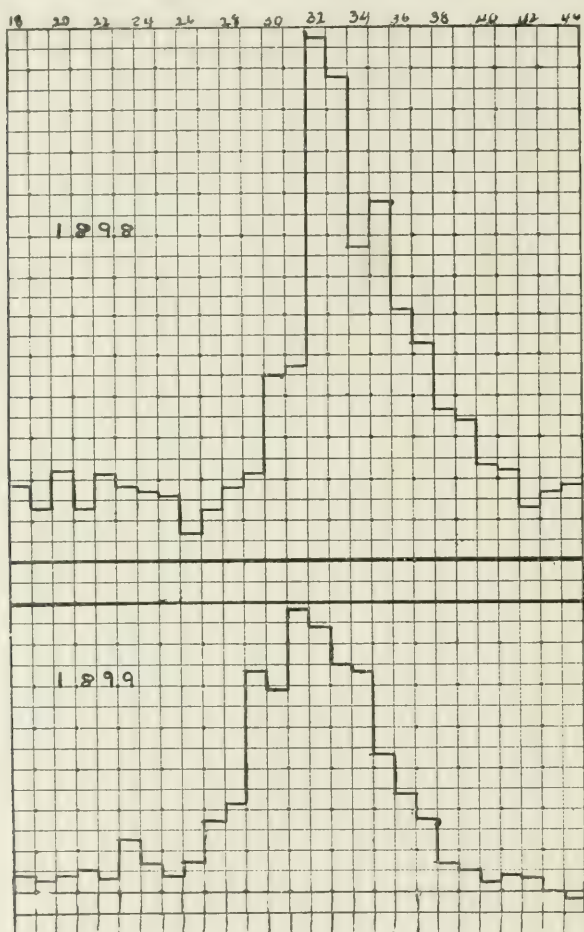


Fig. 16.—Summer diarrhea in Paris. After Budin.

that the mortality is higher after the second day of hot weather, but a special effect on the second and third day cannot be discovered in the curves here presented.

From this study, I must conclude that the direct effect of excessive heat is inimical to infants sick with gastro-enteric diseases, and the mortality is higher in the summer. This is really the common clinical



impression, that diarrhea is more protracted and more fatal in the summer than in winter.

An entirely different question is offered by the prevalence of diarrheal diseases in the summer. Does the excessive heat produce diarrhea by its direct effect on the organism? Miller believed that it does, and Rietschel and others have attempted to prove it. My own study is unequivocally against it.

In the first place, numerous observations on premature infants kept in incubators which have been kept too warm (Budin,<sup>12</sup> Zahorsky<sup>13</sup>) have failed to note diarrheal tendencies. The symptoms are flushing of the

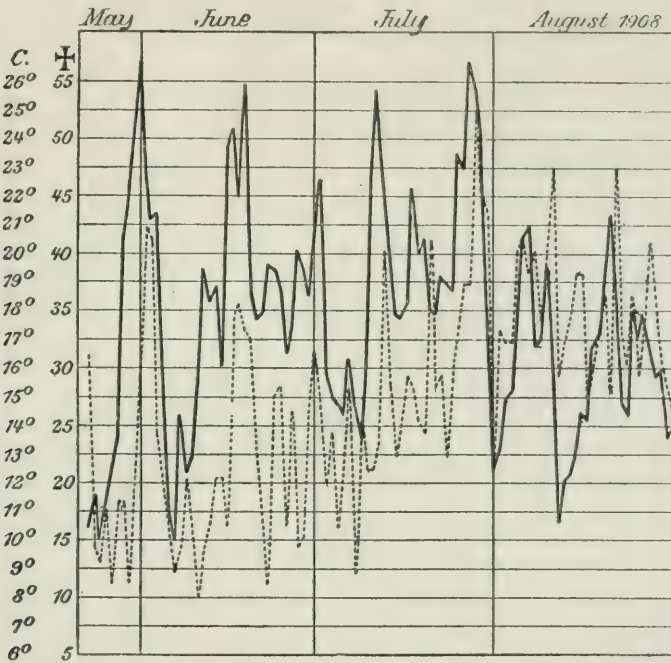


Fig. 17.—The curve of Finkelstein, showing daily deaths and mean temperature in Berlin, 1908.

skin, perspiration, anuria, rapid shallow respiration and an elevation of temperature.

We are familiar with the direct effects of heat on infants in St. Louis. On numerous occasions the temperature in the houses in the last fifteen years has reached 92 to 95 F. The babies lie quiet and the symptoms are the same as those noted in premature infants. A few times conditions have been such as to produce marked thermic fever — even heat stroke — among infants under my observation. A memorable instance occurred in

12. Budin: *Le Nourrisson*, 1900, p. 18.

13. Zahorsky: *St. Louis Courier Med.*, 1905, xxxii, 68.

1897 in the Bethesda Foundling Home. This incidence was referred to briefly in a general discussion on thermic fever in infants (Zahorsky<sup>14</sup>). The records were accidentally destroyed soon afterward and the cases were never properly placed in the literature. To quote from the article mentioned (page 144) :

This summer I had the sad opportunity to witness four fatal cases among the infants at the Bethesda Foundling Home. Altogether about forty cases of marked thermic fever were noted in this institution this summer; and I am convinced that in former years such cases also occurred, but were not diagnosticated as such. On the night of June 11, 1897, an infant had an eclamptic seizure. A few minutes afterward another infant was attacked in the same way. The rectal temperature was 110.6 F. in the one, and 111.4 F. in the other. They were imme-

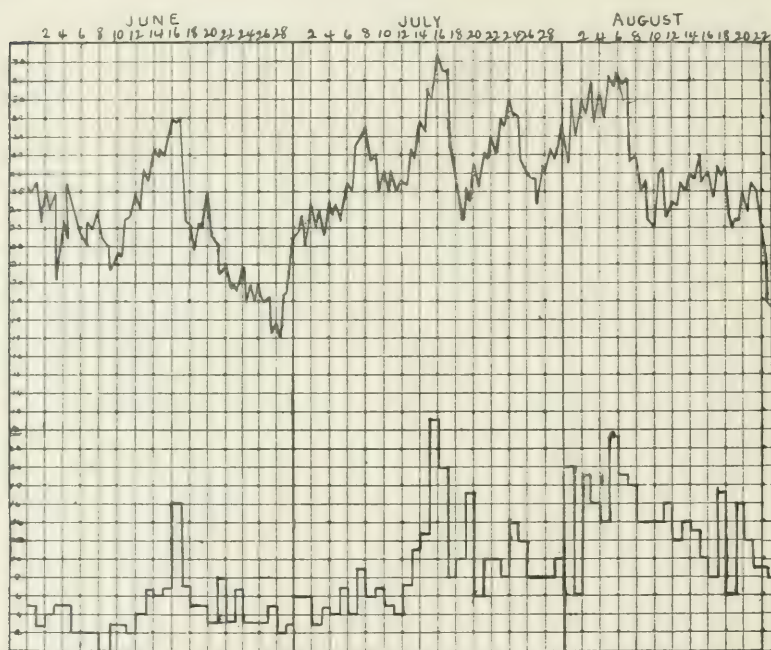


Fig. 18.—After Willim. Mortality from gastro-enteric diseases in Breslau, 1904.

diately placed in a cold bath by the nurses. When I arrived one was dead and the other died in a few minutes, although cold baths and stimulants were freely used. I found at the same time six other infants who had fever ranging from 102 to 107 F.; all these, however, were saved. On careful inquiry and examination no evidence of acute gastro-intestinal infection could be elicited, although vomiting had been a symptom in a few cases.

The post-mortem and blood examination showed clearly that thermic fever only could explain the disease. On the evening of July 8, again several cases occurred and one more death with hyperpyrexia. About one-half of the infants in the nursery during this period of heat showed febrile movement ranging from 101 to 108 F., which could not be attributed to any form of infection. On the

14. Zahorsky: *Pediatrics*, 1898, v, 144.

morning of July 11 the atmospheric temperature fell 15 degrees, and with it all the fever which had persisted for four days in spite of care, disappeared as if by magic. About fifteen cases more, only two hyperpyrexial, occurred during the rest of the summer.

From page 150 another quotation:

The first series of heat strokes that were noticed last summer occurred during the sudden rise of terrestrial temperature June 8 to 12, when in four days the

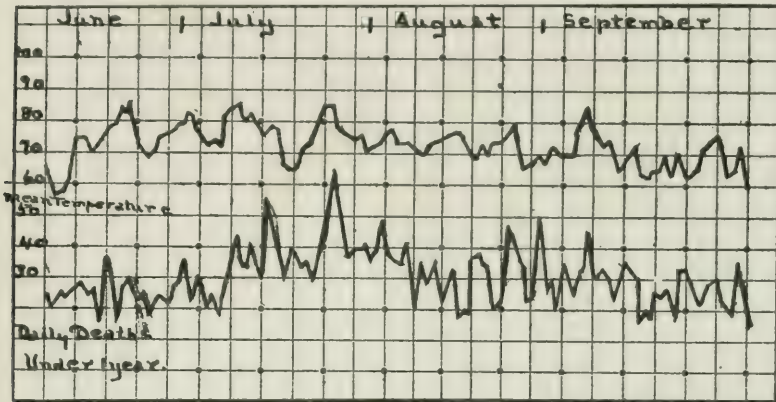


Fig. 19.—Mortality and mean temperature in New York City, 1912.

### Daily Deaths and Temperature, JULY 1911.

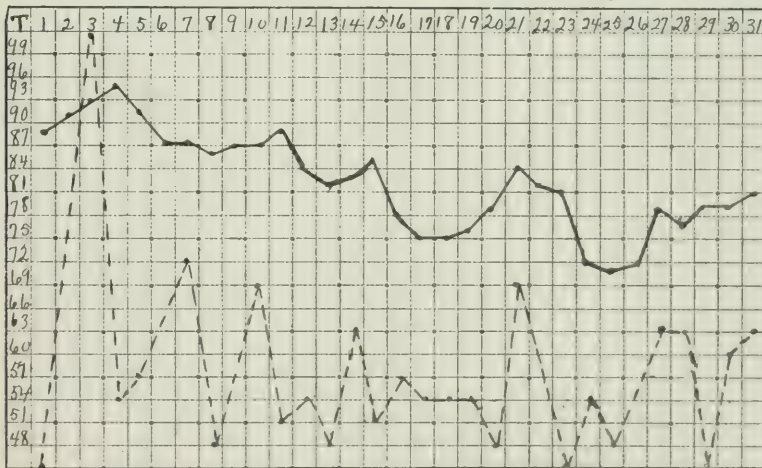


Fig. 20.—Daily mean temperature and deaths from diarrheal diseases in St. Louis, July, 1911.

daily maximum increased twenty-five degrees. It was during this period that two fatal cases occurred at the Bethesda Foundling Home. On June 17 the atmospheric temperature reached 96 degrees and several cases occurred again with one death. One case in private practice was studied at this time. But in this instance the additional heat of a baker's large oven in the basement added



to the temperature. The next series, and most general, occurred July 8 to 11, when in four days the atmospheric heat rose from 89 to 97 F. July 10 was memorable, as thirty babies at this home had temperatures ranging from 100 to 107 F., in spite of the free administration of water and the best of care. The nurses and physicians were constantly busy giving the overheated little ones a bath. July 11 the temperature fell 20 degrees and a remarkable result occurred.

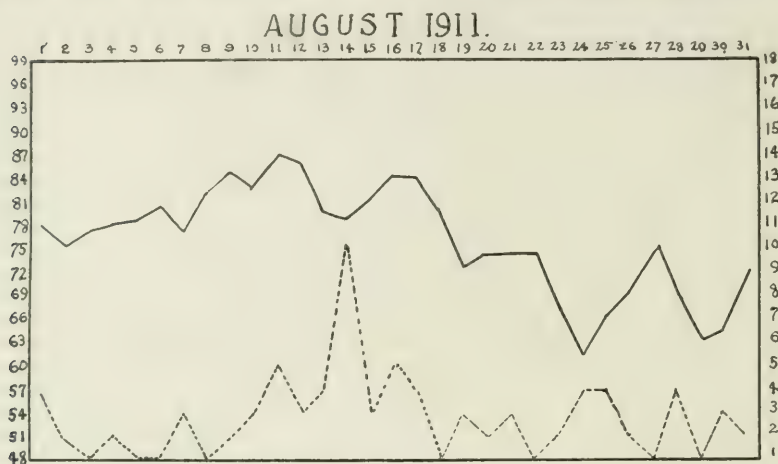


Fig. 21.—Daily mean temperature and deaths in St. Louis, August, 1911.

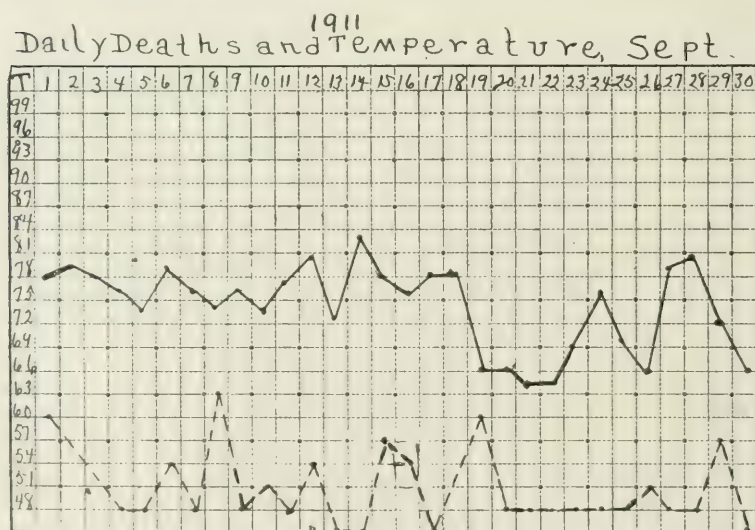


Fig. 22.—Daily mean temperature and deaths in St. Louis, September, 1911.

The thirty infants who had been having febrile movement for three days, some distinctly hyperpyrexial, became free from fever inside of twenty-four hours. This was so striking, and accompanied the fall in general heat so closely, that it forms a powerful argument to sustain the thermic rather than the fermentative causation of the pyrexia. The general average for this period was 88 degrees.



The next cases occurred during the latter part of July and the first week in August. The average mean temperature for this period was 88 degrees again, with a maximum of 97 degrees. Two cases with a temperature of 107 degrees developed. The high temperatures of August and September were not accompanied by thermic fever, although it occasioned, no doubt, more pyrexia among the many cases of gastro-intestinal infection which were treated at that time.

A few years later a similar epidemic occurred in the same institution, but was much less violent. Many times since the rectal temperature of infants on hot evenings has been 1 to 3 degrees above normal, and yet in all these observations no diarrheal tendencies have been observed. Thermic fever and diarrhea are distinct diseases and have little relationship.

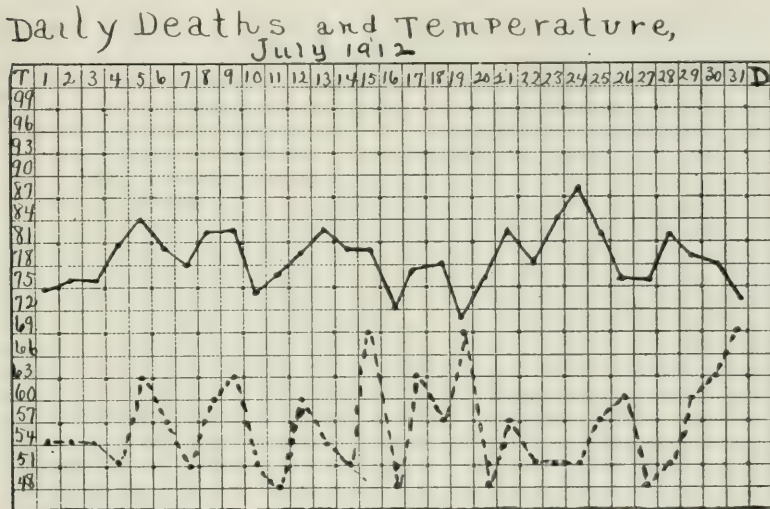


Fig. 23.—Daily mean temperature and deaths in St. Louis, July, 1912.

Experimental evidence against the heat hypothesis is found in the work of Genersich,<sup>15</sup> who ascertained that a room temperature of 28 to 30 C. produced an elevation of the rectal temperature in infants, but no gastro-enteric disturbance was observed. A more exhaustive study by Kleinschmidt<sup>16</sup> had a similar negative result and his studies in metabolism revealed nothing abnormal. He is positive in denying the inimical effect of heat on the digestive apparatus of infants.

Helmholz<sup>17</sup> studied the effect of the temperature of dwellings in Chicago, and the occurrence of diarrhea and published the following

15. Genersich: *Monatschr. f. Kinderh.*, 1910, 183.

16. Kleinschmidt: *Monatschr. f. Kinderh.*, 1910, p. 455.

17. Helmholz: *Tr. Am. Assn. for Study and Prevention Infant Mortality*, 1912.

instructive table. The outbreaks of diarrhea occurred in days with the maximum temperature indicated.

Temperature F. ....	70-74	75-79	80-84	85-89	90-100
Cases .....	7	9	9	5	2
Percentage .....	22	28	28	10	6

He concluded that the heat *per se* was not a great factor in causing diarrhea or fever.

Knox<sup>18</sup> studied the effect of heat in the dwellings in Baltimore without observing any ill effect on the well being of infants.

Alter all, the subject needs a greater study of clinical cases. Acute cases of diarrhea should be studied more carefully as to the mode of

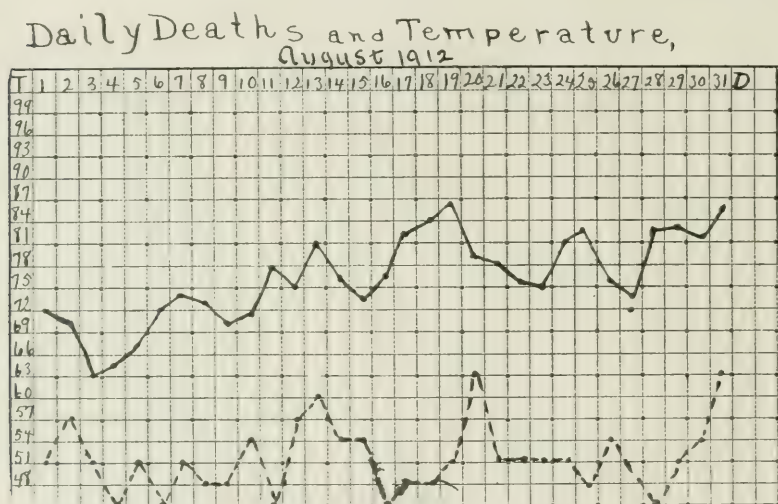


Fig. 24.—Daily mean temperature and deaths in St. Louis, August, 1912.

onset and the attendant atmospheric conditions. In the following are tabulated all the cases seen by me in private practice during the summers of 1911-12. The date of onset is compared with the atmospheric temperature.

	CASES SEEN IN PRIVATE PRACTICE					
Mean temperature ..	61-65	66-70	71-75	76-80	81-85	86-90
Cases .....	5	12	12	38	29	13
The ratio .....	1.0	1.4	1.4	7.6	5.8	2.6

If we find the ratio of the number of days with the above temperatures to the number of days in the whole period which is as follows:

1          1.3          2.7          4.3          3          1

the conclusion is inevitable that more cases of diarrhea occur during the warm days, but the greatest number occur when the mean temperature is

18. Knox: Tr. Am. Assn. for Study and Prevention Infant Mortality, 1912.

between 75 and 80 F. The number of cases, however, is too small to draw any positive conclusions.

My experience with cases of thermic fever reveal the fact that it is the older infants—6 months to 15 months—who suffer the most severely from the heat. Thus in the epidemic mentioned, younger infants did not react at all or much less. This was attributed at the time to the fact that the older infants received undiluted cow's milk, a food having a high nutritive ratio, while the younger infants received diluted milk. That is, in hot weather a food very rich in protein predisposes to hyperthermia. This is only the rational deduction from physiologic principles, since the body has no storehouse for protein. However, at the time when our older infants were reacting with the remarkable cases of hyperthermia, no diarrheal tendencies were observed among the younger infants.

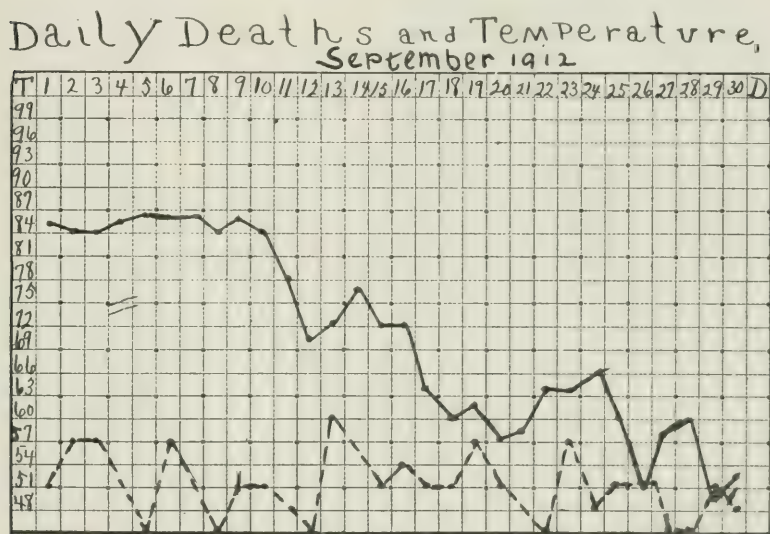


Fig. 25.—Daily mean temperature and deaths in St. Louis, September, 1912.

A study of the mortality from the Bethesda Foundling Home is appended. The mortality for the whole time is shown in Figure 29. The mortality after pasteurized milk and effective refrigeration methods were adopted was much less. We have had some diarrhea since adopting these measures, but none of the severe epidemics which almost wiped out all our babies in previous years. We have had some very hot weather in the last five years, and cases of hyperthermia have occurred, but all severe forms of diarrhea were absent.

A single example of diarrhea apparently produced by excessive heat alone is exhibited by Rietschel, but the clinical and experimental evidence is overwhelmingly against him.

The form of the disease which is mostly to be feared is the dysenteric type, commonly grouped under the name of ileocolitis, or infective diarrhea. Here the protracted febrile cause, in spite of favorable changes in temperature, the character of the stools, the high mortality and post-mortem findings plainly demonstrate its infectious origin. What per cent. of the whole number of cases are caused by this infectious form is not known, but judging from my own experience the majority of deaths in infants over 6 months of age are traceable to these infections. The typical cholera infantum is rare.

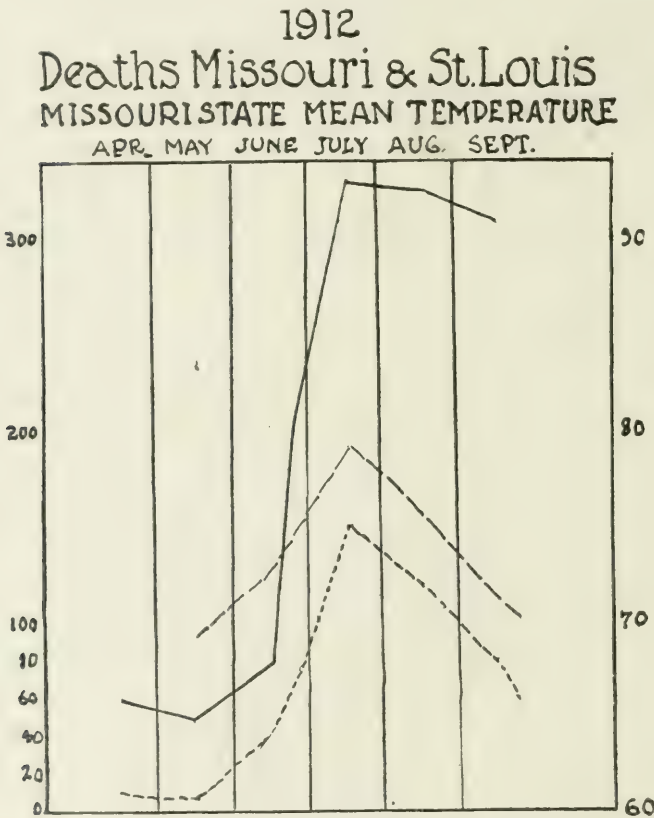


Fig. 26.—Curves comparing the deaths in Missouri State and St. Louis City.

The only forms of summer diarrhea which might be induced by excessive heat are the fermental diarrheas and the intoxications. Even in these cases the evidence that heat alone is more than a predisposing cause is altogether insufficient.

In the early period of July the correspondence between the height of the temperature and the morbidity is very striking. This parallelism may be observed in Figure 20. It is less marked in August or September.



In general, the high basal line of mortality corresponds to the increase in diarrheal diseases in the summer as shown in the curve drawn from Seibert's figures. The sharp elevations correspond to the increased mortality produced by the heat. Liefman and Lindeman's studies have accentuated the sharp distinction which should be made between the basal line and the sharp elevations in the mortality curve. Contrary to their teachings I do not find that these elevations are produced by heat-strokes. They are the expression on hot days of an increase in deaths occurring in infants already fatally ill. The high basal line is a good index of the

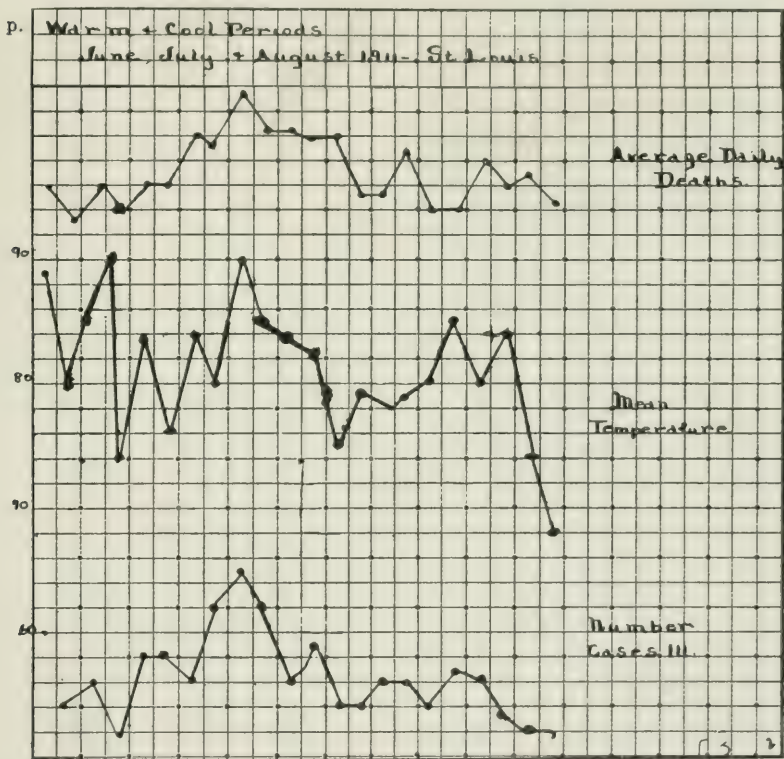


Fig. 27.—The lowest curve represents the number of cases of diarrhea beginning at each period. Taken from the St. Louis mortuary records.

morbidity. For example, in September, 1912, in spite of a marked fall in the terrestrial temperature, deaths from diarrhea had not ceased, and, as proved in my private practice, new cases continually occurred. Thus in August I saw fifteen new cases, and in September also fifteen new cases, half of which were observed during the last two weeks when the temperature was low.

In fact, in St. Louis we recognize an autumn diarrhea coming on in the latter part of August and running through September and October.

These cases are characterized clinically by the passage of small, mucous stools, moderate fever, and a protracted course. The symptoms are those of an infectious colitis, and do not yield promptly to an antifermentative diet. On the other hand, the cases in July, excepting those grouped under the term of ileocolitis, exhibit a marked tendency to watery stools.

Rietschel and others have tried to find an etiologic relation between the dryness of the atmosphere and infant mortality. In fact, stress has

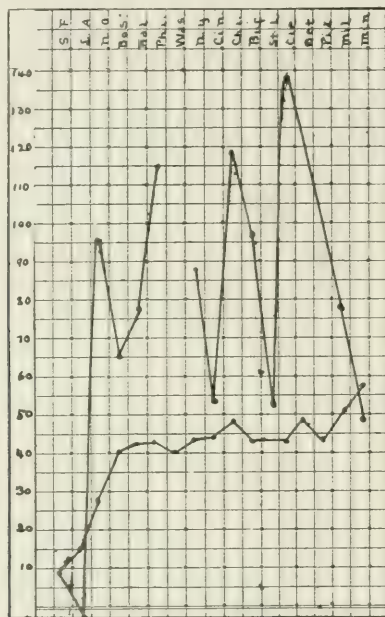


Fig. 28.—The lower curve represents the difference between the mean winter and summer temperatures; the upper curve gives the death-rate (1910) in the cities shown by the initials in the top line. It is true that the cities with the least difference show the least mortality.

been laid on the exsiccation of the tissues in the sick baby as a factor in infantile mortality. As a matter of fact, however, it is the hot humid days which cause the most cases of thermic fever.

TABLE 3.—AGES OF INFANTS DYING OF SUMMER DIARRHEA IN ST. LOUIS IN 1911 AND 1912

Age	Cases	Age Months	Cases	Age Months	Cases
1 Month or less .....	53	10	24	19	7
2 Months .....	75	11	20	20	8
3 Months .....	58	12	19	21	9
4 Months .....	60	13	18	22	3
5 Months .....	47	14	17	23	4
6 Months .....	42	15	8	24	3
7 Months .....	36	16	7	25	4
8 Months .....	34	17	7	26	3
9 Months .....	36	18	12	27	2

These figures emphasize the point that the second summer is not the most dangerous. Yet to the infant who has been nursed the first summer the second summer offers considerable danger. Clinical experience teaches that nearly every infant during the first and second years has one or more attacks of diarrhea. There is no disease so universal. While much stress is laid on the fact that deaths from enteritis are rare among the well-to-do, the prevalence of diarrhea among these babies does not seem to be much less than among the poor. But among the former the prompt recognition and therapy reduces the mortality to a very small figure.

While the death-rate in the country is usually less than in the cities, the babies there almost universally have diarrhea the first or second summer (personal observation).

A few additional facts may be offered on this subject.

In the summer of 1898 about 100 babies, inmates of the Bethesda Foundling Home, were taken out of the asylum and placed in an adjoining building while the asylum was fumigated for some contagious disease. This building was not screened and flies literally covered the babies all day. Two days later an epidemic of diarrhea commenced which carried off twenty-seven of the inmates in the next thirty days.

In July, 1905, all the infants were fed on raw milk of exceptional purity; nevertheless, an epidemic of dysentery occurred. More than forty infants were attacked, and fully half of them died. The disease was characterized by bloody, mucous stools and protracted fever.

At least three times I have seen severe forms of diarrhea introduced among infants in institutions by an infant from the outside sick with diarrhea.

It is useless to multiply instances or reports from other sources. We recognize in America a common form of diarrhea that has all the clinical characters of an infectious disease; that is communicable and transmitted by flies, milk and other foods; that is independent of hot days, and makes up a very large part of the deaths from summer diarrhea. To argue that heat alone by its direct effect on the organism produces the great increase in the morbidity and mortality is to deduce a general law from very few facts.

#### CONCLUSIONS

1. The mortality of summer diarrhea is practically the same all over the United States. The only marked exceptions are certain cities on the Western Coast.

2. The mortality of diarrheal diseases is twice as high in the summer as in the winter.

3. A room temperature of more than 85 F. has a detrimental influence on the sick baby.

4. Hyperthermia may be produced in infants when the day and night temperature is more than 85 F., but this thermic fever does not produce diarrhea nor appreciably raise the mortality rate.

5. Summer diarrhea is not the effect of high atmospheric temperature alone, but it cannot as yet be denied that excessive heat may lower the tolerance to carbohydrates and other elements of food.

6. We must seek the cause of summer diarrhea (1) in micro-organisms whose virulence and activity may be increased in the summer; (2) in endogenic or ectogenic toxic substances of unknown nature.

1460 South Grand Avenue.



# THE INFLUENCE OF ATMOSPHERIC CONDITIONS ON THE MORTALITY OF INFANTS SUFFERING WITH GASTRO-INTESTINAL DISORDERS

A STUDY OF THE SUMMERS OF 1910, 1911 AND 1912 IN ST. LOUIS \*

A. S. BLEYER, M.D.  
ST. LOUIS, MO.

Description of Charts: The heavy upright lines in the charts (pp. 321-2-3) represent the total number of deaths from non-surgical disorders and diseases of the gastro-intestinal tract which occurred among infants in the first two years of life in St. Louis on each day of the months May, June, July, August and September of the years 1910, 1911 and 1912 (deaths in the first week of life were not included). Each horizontal space denotes one death. The numerals at the left and right margins refer to degrees of heat and relative humidity and also to average miles per hour of wind velocity.

The heavy horizontal line represents the mean of the daily maximum and minimum temperatures.

The shaded horizontal line represents the mean relative humidity for each day as determined by averaging the relative humidity at 7 a. m. and 7 p. m.

The horizontal line at base of charts represents the average wind velocity per hour for each day.

(Temperature, relative humidity and movement of air were computed from records at the U. S. Weather Bureau at St. Louis. Deaths were compiled from death certificates at the mortuary office of the St. Louis Health Department.)

As for humidity, the charts for St. Louis seem to coincide with studies conducted in other cities, notably those of Willim for Berlin and Breslau; in none could a definite relation between humidity and summer deaths among infants be shown.

The St. Louis charts show that quite often the most intimate relation between heat and deaths may exist during periods of low humidity; an instance of this may be seen in the rise of the death-curve in Chart 1 (1910), which set in about the middle of June, when the humidity was low, and remained low until the death-rate had acquired its usual summer level. This is still more strikingly seen in Chart 2, the excessive heat of 1911 continuing throughout June and July, presenting the highest death-curves of the three summers and being attended by a singularly low relative humidity. (In corroboration, it was interesting to find that curves taken in New York City during the past several summers show also that a low humidity often accompanies a high death-rate in the presence of high temperatures.) Instances illustrating the converse of this proposition are found several times in these St. Louis charts and

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\* Read at a meeting of the Washington University Medical Society, May 12, 1913.

show that the death-rate may be surprisingly low during excessively moist periods, even when the temperatures were high. Elevations of temperature above 71 or 72 F. were, as a rule, soon followed by a rising death-curve regardless of the presence or absence of high relative humidity.

As for the influence of heat on infant deaths from gastro-intestinal disorders, a glance at any charts of this sort will show at once that a strong relation exists; there is an obvious although imperfect parallelism between the temperature-curve and the death-curve. It was chiefly for the purpose of studying this relation that the present work was undertaken.

The nature of the influence of high temperatures on infant deaths, of those infants particularly who are suffering from gastro-intestinal disturbances, is far from clear. A view which has attracted a considerable amount of attention during the past two years is based on the assumption that heat may produce so profound an alteration of metabolism as to be followed within a few hours by death. This so-called "heat-stroke" theory was evolved not from clinical observation, but from the study of mortality charts such as are here presented; they differ from these, however, in the very salient fact that for the most part 2:00 p. m. temperatures or maximum temperatures were used, whereas in the St. Louis charts, mean temperatures for each twenty-four hours were selected.

In the case of adults, heat-stroke is clinically well known, and similar if not identical conditions have been produced experimentally in monkeys by exposing them to the sun (Aron, Philippine Islands); among infants, however, heat-stroke has not been commonly diagnosed, and if the contention made by Liefmann and Lindemann, the originators of this theory, is correct, many deaths which have been ascribed to toxic degenerations of liver or heart or to alimentary intoxications were, to be more accurate, heat-strokes.

In order to study the acute rises in deaths coincident with similarly acute rises in temperature, Liefmann and Lindemann used the terms "death-peaks" and "heat-peaks." In the present study an "heat-peak" was assumed to be the summit or climax of any ascending daily mean temperature, starting at not less than 70 degrees. During the summers 1910, 1911 and 1912 such "heat-peaks" occurred in St. Louis forty-one times; "death-peaks" coincident with these "heat-peaks" occurred in nine, 22 per cent., of instances; or, to place it the other way 'round, coincident with 78 per cent. of the "heat-peaks," the death-curve either remained stationary or dropped.

According to Finklestein, Klose and others, a more striking effect of high temperatures may be observed on the day following the summit of the heat-wave. This I found to be the case in 24 per cent. of instances; lastly, the third day was represented by 15 per cent. Further than this

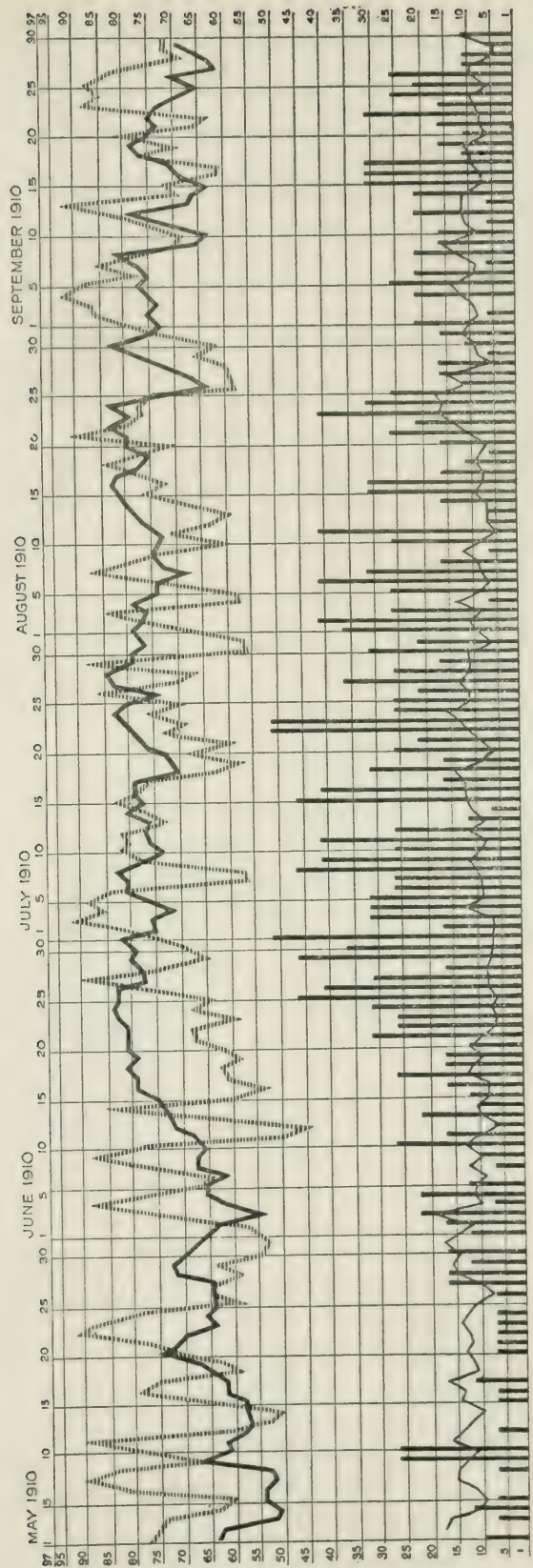


Chart 1



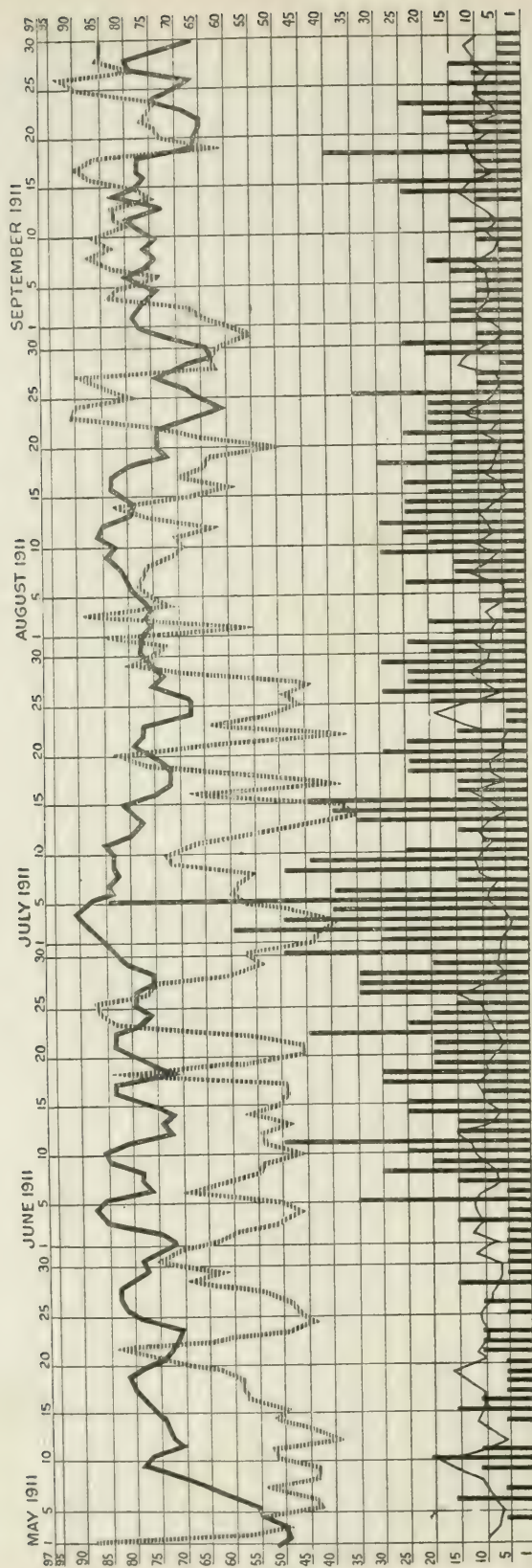


Chart 2



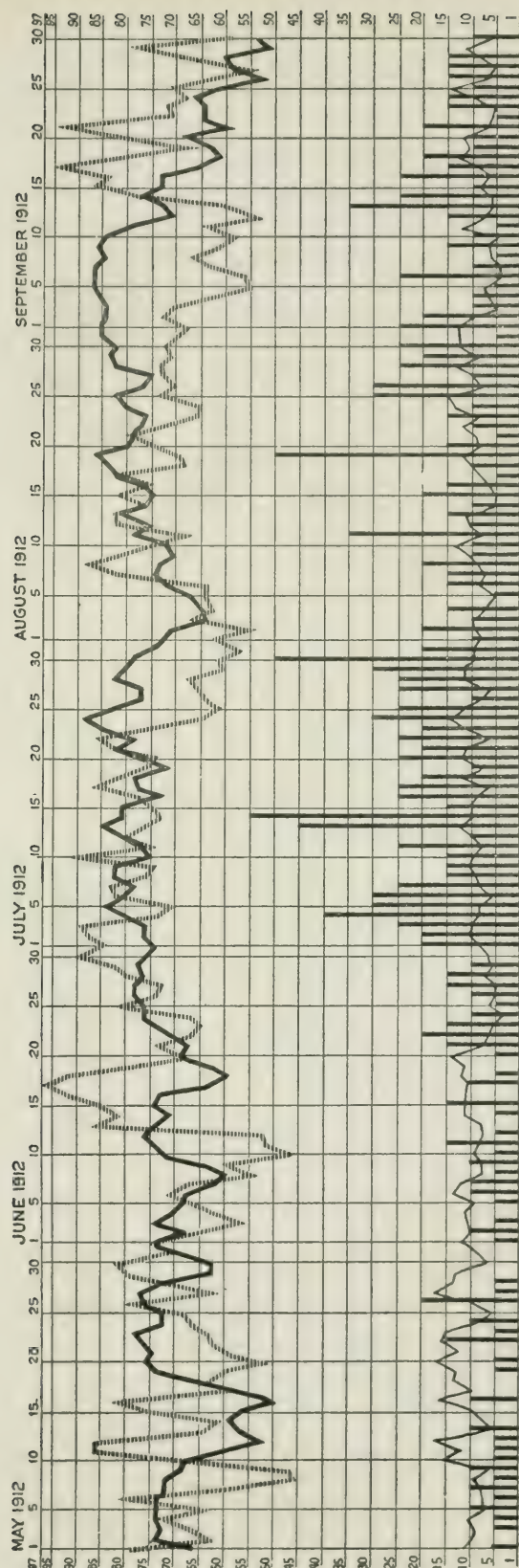


Chart 3

it was not possible to go because of the occurrence of new and conflicting "heat-peaks."

Because of these low figures it was sought to determine the behavior of the death-curve in relation to accessions of heat to points above 70 F., that is, the behavior of the death-curve was noted whenever the mean temperature reached 70, 75, 80, 85 and 90 F. This method revealed ninety-six instances in the three summers, and it was found that, corresponding with the day of the heat accession, the deaths went up in 27 per cent. of instances, that on the day after the accession it rose in 34 per cent. of instances and on the third day in 20 per cent. of instances. It is noteworthy, moreover, that the elevations of the death-curve on extremely hot days was less frequently noted than on those days when the temperature was not so high, as is seen in the following summary:

BEHAVIOR OF DEATH-CURVE IN RELATION TO ACCESSIONS OF MEAN TEMPERATURE  
TO 70, 75, 80 AND 85 F., SUMMARY OF NINETY-SIX INSTANCES  
IN 1910, 1911 AND 1912:

AT 70 DEGREES: In eighteen instances of accession to 70, the death-curve rose on the first day, four times; second day, seven times; third day, three times. In four of these eighteen instances the death-curve fell on the day the mean temperature reached 70 F.

AT 75 DEGREES: In thirty instances of accession to 75, the death-curve rose on the first day, eleven times; second day, eight times; third day, four times. In five of these thirty instances the death-curve fell on the day the mean temperature reached 75 F., and in two instances it remained stationary.

AT 80 DEGREES: In thirty instances of accession to 80, the death-curve rose on the first day, eight times; second day, thirteen times; third day, eight times. In six of these thirty-six instances the death-curve fell on the day the mean temperature reached 80 F., and in one instance it remained stationary.

AT 85 DEGREES: In twelve instances of accession to 85, the death-curve rose on the first day, three times; second day, four times; third day, four times. In one of these twelve instances the death-curve fell on the day the mean temperature reached 85 F.

In ninety-six instances the death-curve dropped or remained stationary in twenty instances; the rise of the death-curve on the day of the accession of heat was more frequent at 75 F., than at 80 F., or 85 F.

In studying the relation of heat to deaths, the originators of the heat-stroke theory found this relation to be most evident in the early summer months. Some of the German charts show this very nicely, but the charts for St. Louis do not show so great an intimacy between heat and deaths in the early months as they do in the later months of the summer; for example, in 1910, the first death-rise in May is not accompanied by a coincident rise in temperature, and a fall in temperature precedes the death-rise of May 27-30. Again, the rising death-curves of early June accompany a really low temperature, but were preceded by moderate heat a week earlier. The fastigium of heat of middle and late June is followed rather than attended by the rising deaths, and such relations may also be seen, although to a less definite degree, elsewhere in

the chart for this year. In the 1911 chart it may be noted that the deaths follow rather than accompany the excessive heat of June and July, although it had already been so extremely hot for so long a time that the curves become confused. Lastly, the rise in deaths in late September accompany a lowered temperature curve, but follow a higher preceding one. In 1912, the deaths of late June are apparently more closely related to the heat of middle June than to that of late June, and this is again seen in the rise of late September in the presence of very low temperatures, following, however, the very high temperatures earlier in the month. It would appear that the death-curve exhibits a sequential rather than an accompanying rise to the heat-curve, the hot days often passing without leaving an immediate impress in deaths.

As for the relation of wind velocity to infant mortality in summer, the subject may be dismissed at this time with a word — no relation could be made out. This does not mean that a relation does not exist, since to the contrary, it has been shown that movement of air is capable of prolonging the lives of animals exposed to the sun; but the charts do not show this.

#### CONCLUSIONS

A definite relation between atmospheric heat and deaths among infants suffering with gastro-intestinal disturbance exists; at what degree of heat lethal effects are seen does not appear in these charts.

A. So-called "heat-peaks" or short-lasting but excessive temperatures doubtless emphasize, but they do not dominate the summer infant death-rate; whether many of these deaths are the direct result of "heat-stroke," although easily supposable, has not been shown.

B. Continuous heat shows a stronger relation, although not necessarily an immediate relation, to deaths of infants suffering with gastro-intestinal disorders, which, as infants are now housed and fed, is very fairly constant.

I wish to thank Mr. Montrose Hayes, Chief of Weather Bureau at St. Louis, for assistance in compiling material for the charts.

Delmar Building.

THE COMPLEMENT FIXATION REACTION OF THE BLOOD  
OF CHILDREN AND INFANTS, USING THE  
BACILLUS ABORTUS AS  
ANTIGEN \*

W. P. LARSON, M.D., AND J. P. SEDGWICK, M.D.

MINNEAPOLIS

The passage of substances through the intestinal wall, and the effect of the ingestion of biologically active bodies on the reactions in the blood and other tissues has been a subject of much interest to many, and especially so to pediatricists. We hope to throw some light on this problem by the demonstration of the fact that a specific reaction can be obtained in the blood of a considerable number of children.

The specific reaction in question is that of the complement fixation test, using the bacillus of infectious abortion of cattle as an antigen. The significance of this particular reaction becomes apparent when we consider that epidemic abortion is common among cattle; that the presence of the *Bacillus abortus* can be demonstrated in cow's milk, and that the reaction is seemingly specific.

The discussion concerning the enteral absorption of homologous or heterologous proteins has been, and still is, of great interest, but if we turn at once to the subject of the effect of the ingestion of biologically active substances, such as toxins and antitoxins joined with proteins, several illuminating studies are at our disposal.

Römer<sup>1</sup> was able to show in 1901 that a colt, the blood of which at birth was found to be antitoxin-free, and which was fed with its mother's milk which contained diphtheria antitoxin, then gave proof of having antitoxin in its own blood. After the twelfth day, however, no further antitoxin absorption could be demonstrated, and the antitoxin content of the colt's serum then rapidly decreased.

This is of especial interest in connection with the position taken by von Behring concerning other proteins and the tuberculosis question, suggesting the greater possibility of absorption of such products by the new-born.

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\* Read before the Chicago Pediatric Society, April 21, 1913, and before the American Association of Medical Milk Commissions, at the Seventh Annual Meeting, held at Minneapolis, June, 1913.

\* Attention is directed to the paper of Dr. E. C. Schroeder in this issue containing comments on *Bacillus abortus*.

1. Römer: Untersuchungen über die intrauterine und extrauterine Antitoxinübertragung von der Mutter auf ihre Deszendenten, Berl. klin. Wchnschr., 1901, xxxviii, 1150.



Salge<sup>2</sup> gave antitoxic horse serum by mouth to human infants. In no instance was he able to demonstrate the passage of the antitoxin into the infants' blood, even in the new-born. When, however, the antitoxic horse serum was injected subcutaneously into the mother or nurse, and the child put to the breast, the passage of the antitoxin to the child's blood could be shown.

Uffenheimer experimented with the administration of serum-hemolysin, casein, egg-albumin, diphtheria and tetanus antitoxins, by mouth, to new-born guinea-pigs. The hemolysin and casein did not pass over. The egg-albumin could be demonstrated in traces only. The antitoxins could, however, be demonstrated in the blood of the new-born pigs.

The recent work of Hehn taken with that of Lust<sup>3</sup> indicates that antitoxins in heterologous serums are absorbed more readily in certain diseased conditions of the alimentary tract.

As the infectious abortion of cattle is a condition which, although well known to veterinarians, has but recently appeared in medical literature, a discussion of the condition may be of value.

The *Bacillus abortus*, often referred to in the literature as the cocco-bacillus of Bang, was discovered in 1896 by Bang and Stribolt of Copenhagen.

Epizootic abortion has for the past century been the greatest curse with which stock-breeders and dairymen have had to contend. For nearly one century scientific men have recognized the contagious character of this disease, but thus far no advance has been made by way of combating contagious abortion either prophylactically or therapeutically.

With the dawn of the bacteriologic era began the hunt for the etiologic agent of contagious abortion. Men so eminent as Nocard worked on the problem not less than three years without being able to throw any light on its etiology.

The discovery of Bang<sup>4</sup> and Stribolt was soon confirmed by Stockman and McFadyean<sup>5</sup> of Great Britain and Nowak<sup>6</sup> of Austria, and more recently the cocco-bacillus of Bang has been found in this country.

#### BACILLUS ABORTUS BANG

Bang's bacillus belongs to the smallest of the visible micro-organisms, measuring from 1 to 2 microns in length. It is a non-motile, non-spore-bearing cocco-bacillus, one diameter being only slightly greater than the

2. Salge: Immunisierung durch Milch, *Jahrb. f. Kinderh.*, 1905, lxi, 486.

3. Lust: Die Durchlässigkeit des Magendarmkanals für heterologes Eiweiss bei ernährungsgestörten Säuglingen, *Jahrb. f. Kinderh.*, 1913, lxxvii, 243.

4. Bang: *Ztschr. f. Tiermed.*, 1897, i; *Maanedskrift f. Dyrlaeger*, 1900.

5. McFadyean and Stockman: Report of Committee to Inquire Into Epizootic Abortion, London, 1909.

6. Nowak: *Ann. de l'Inst. Pasteur.*, 1908, xxii, 541.

other. It may readily be stained by any of the ordinary anilin dyes, but is Gram-negative.

The micro-organism in question will grow on any of the ordinary culture media after it has once been cultivated in the laboratory. Bang and Stribolt noticed that the growth of the *Bacillus abortus* appeared a few millimeters beneath the surface of the culture medium and hence concluded that it was a semi-aerobe, developing only at such a point as presented a given oxygen pressure. These authors made the further observation that after this micro-organism had once been cultivated in the laboratory succeeding generations thrived best in an atmosphere of nearly pure oxygen.

McFadyean and Stockman found that the *Bacillus abortus* could be cultivated successfully when grown in symbiosis with the *Bacillus subtilis*. These authors assumed that the *B. subtilis* by absorbing a part of the oxygen contained in the closed chamber created a favorable atmosphere for the development of the *B. abortus*. If the observations of these European authors are correct relative to the *B. abortus* in its relation to oxygen, we have here a phenomenon quite unique. It seems strange that an organism which in the first generation develops only under conditions of diminished oxygen pressure should swing to the opposite extreme in the succeeding generation.

There is another possible explanation of this, however.

All who have worked with this organism will agree that the growth of the first generation on artificial media is slow. The colonies, as a rule, do not appear until at the end of the fourth or fifth day, and sometimes even eight to ten days may elapse before the growth becomes apparent. During this time the surface of the culture medium has a tendency to dry out and the growth appears deeper probably because of its demand for moisture.

We have further found that the *B. abortus* grows very well on the surface of ordinary slant agar provided the tube is well sealed with paraffin to prevent evaporation. In a previous paper<sup>7</sup> we have expressed the view that this *might* be explained by the fact that agar absorbed a part of the oxygen contained in the tube, thus creating a favorable environment for the development of the *B. abortus*.

When Bang's bacillus has once been cultivated in the laboratory it grows readily on any of the ordinary media.

The isolation of the *B. abortus* presents but few difficulties. It will, as a rule, be found in pure culture in the gastro-intestinal tract of the fetus provided this is obtained within a few hours after it has been expelled.

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7. Larson, W. P.: Jour. Infect. Dis., 1912, x, 178.

TECHNIC OF CULTIVATION OF *B. ABORTUS*

The technic we employ is to inoculate tubes of slant agar, preferably ascitic agar or serum agar, from the gastro-intestinal tract of the fetus, and either seal the tubes with paraffin or place in a closed flask together with a few tubes of slant agar freshly inoculated with the *B. subtilis*. On the fourth or fifth day, occasionally on the third day, the growth on the surface of the medium is apparent in the form of small dewdrop-like colonies, which at first remain isolated, but in the course of the next few days become confluent. The *B. abortus* does not coagulate milk nor liquefy gelatin. It produces neither acid nor gas on any of the sugar media. On potato it resembles very much the *B. malleus*.

It has until quite recently been held that the bacillus of Bang was not pathogenic for any of the laboratory animals, with the possible exception of mice. The work of Smith and Fabyean<sup>8</sup> and Schroeder and Cotton<sup>9</sup> shows that this organism is pathogenic for guinea-pigs. Injected intravenously into pregnant rabbits or guinea-pigs it will often interrupt pregnancy.

Smith and Fabyean<sup>8</sup> have recently found that when injected into the peritoneal cavity of guinea-pigs the bacillus of Bang produces lesions very similar to those of tuberculosis. They report observations made on fifty-eight guinea-pigs and they found lesions in the following organs: lymph-nodes, spleen, liver, kidney, testicle, lung, bones. The eyes of some of these animals presented lesions in the form of an opacity of the cornea.

Fabyean<sup>10</sup> found further that the guinea-pigs thus affected were hypersensitive to a toxin extracted from the cultures of the *B. abortus*, even when injected in small doses, causing the death of the animals in from twelve to forty-eight hours, thus resembling the action of tuberculin when injected into tuberculous animals.

In the summer of 1911 we became interested in contagious abortion of cattle and inaugurated studies of the disease as it affects bovines. Our work was directed mainly toward establishing the identity of the American and European diseases by the complement-fixation method.

Wall<sup>11</sup> and Holt,<sup>12</sup> working in the laboratory of C. O. Jensen of Copenhagen, had found that contagious abortion of cattle could be accurately diagnosed by this method. We were able to confirm their work. We found that antigen prepared from cultures of the *B. abortus* received from Denmark fixed the complement in the presence of serum

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8. Smith and Fabyean: Centralbl. f. Bakteriöl., lxi, 549.

9. Schroeder and Cotton: Leaflet issued from the Bureau of Animal Industry, 1912.

10. Fabyean: Jour. Med. Research, xxi, 441.

11. Wall: Maanedskrift f. Dyrlaeger, 1910, xxi.

12. Holt: Maanedskrift f. Dyrlaeger, 1911, xxii, 1.



from an infected animal. Cultures which we isolated from infected material in this country were identified with the Danish organism.

We have, during the past two years, had occasion to examine the blood of several hundred animals and have found the complement-fixation method to be a very accurate means of diagnosing this disease.

Epizootic abortion is probably the most prevalent of all animal diseases. There is scarcely a dairy community where the disease has not at some time prevailed. Young heifers of the herd are the first to become infected and abort. Once introduced into a herd it passes from animal to animal until nearly the entire herd has become infected. An animal will usually abort two to three years in succession, after which she is apparently immune, and when not made sterile by the disease, will carry to term. The abortions usually occur from the third to the seventh month of gestation. The general health of the animal is apparently undisturbed by an infection with the Bang bacillus.

It is generally supposed that the male element of the herd transmits the disease from animal to animal, but there is at present no definite proof of this. Cultures made from bulls of infected herds have invariably been negative; likewise blood examinations made on some fifty bulls have all given negative results.

Bang was able to cause cattle, sheep and goats to abort by administering cultures of the organism per os.

Owing to the prevalence of the disease one would naturally expect to find the organism in milk.

In a study of the pathogenic organisms found in milk, Schroeder and Cotton accidentally found the *B. abortus*, but for some time were not able to identify it. They injected milk as obtained on the market into the peritoneal cavity of guinea-pigs and not infrequently found tubercle-like lesions of the abdominal viscera following such injections in about 10 per cent. of the animals thus treated. They finally concluded that the lesions were due to the *B. abortus*.

It has been pretty conclusively demonstrated that all of our domestic animals are susceptible to infection by this organism, although cattle are by far the most frequently affected. Bang found that sheep and goats would abort after being experimentally infected with this organism. Ostertag<sup>13</sup> isolated the organism from mares which had aborted. The usual laboratory animals are likewise susceptible to this disease. About one year ago we were forced to discontinue our complement-fixation work on this disease owing to the fact that fully 60 per cent of our guinea-pigs gave a positive reaction, in consequence of which their serum could not be utilized as complement.

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13. Ostertag: Kolle and Wassermann's Handbuch d. path. Mik.



## HUMAN INFECTION

While we were making field observations we took particular pains to make inquiries as to whether there had occurred abortions in women who had come in contact with a herd of cattle while an epidemic of contagious abortion prevailed. Such observations would naturally be of but little value unless one had the opportunity of observing a large number of cases. In the limited number we have had occasion to observe, we have recorded cases of abortion of the mother of the household where the ordinary causes, such as lues or injuries, could be definitely excluded. The results of our investigation along this line will be presented in another paper. Suffice it to say that in systematically examining the serum of women who have aborted we have found that a larger number give a positive complement-fixation reaction using the *B. abortus* as antigen than when the ordinary syphilitic antigen is used.

Thus having evidence indicating that humans might become infected with this organism, we proposed to carry our investigation further in the hope of determining whether or not and to what extent the micro-organism in question might be of pathological significance to the human family.

As indicated elsewhere in this paper, the bacillus of Bang is somewhat difficult to cultivate, especially when found in impure culture. In view of this fact the ordinary bacteriological procedures did not appeal to us as being the most desirable as exploratory measures; hence we then proposed to push our investigations further by means of the complement-fixation reaction.

From the work of Cotton and Schroeder we know that 10 per cent. of market milk contains the *Bacillus abortus*; there can, therefore, be little doubt that any individual using dairy products is amply exposed to infection. Bang has shown that animals may readily be experimentally infected with this organism by administering it per os. If the *B. abortus* is pathogenic for human beings, as it is for guinea-pigs, and can be transmitted through the digestive tract as is the case with cattle, we would expect infants and children to be the subjects most frequently infected. We have to date examined the blood of 425 children by the complement-fixation method and have found at least some support of the above-expressed hypothesis. Of these 425 cases we found seventy-three positive and 352 negative reactions. In other words, the blood of 17 per cent. contained antibodies against the *B. abortus*. The same technic was used as in the examination of bovine serums. In order to guard against every possible source of error, known positive and known negative bovine serums were invariably used as controls. Our work was not confined to the complement-fixation test, but agglutination tests were made in a large number of cases. We found in working with human serum, as did Holt

with bovine serum, that the agglutination and complement-fixation tests run parallel.

To further corroborate the evidence that we were dealing with specific antibodies, other methods suggested themselves. In their work on hemolysis, Ehrlich and Morgenroth found that the specific hemolytic antibodies would unite with the washed erythrocytes when the latter were placed in the serum and left for a few hours. By centrifuging this mixture and decanting off the supernatant serum they found that the latter had, by the contact with the blood-cells, been depleted of the hemolytic antibodies. In other words, the antibodies had attached themselves to the blood-cells and been removed with these.

The same is true of the *B. abortus* antibodies. By treating a positive serum with a suspension of the Bang bacillus, the serum, after a few hours' contact, has been found to be negative when separated from the organisms by the centrifuge. If an adequate amount of complement is then added to the sensitized bacilli and incubated for an hour, the complement will become fixed, thus indicating further that we are dealing with specific antibodies.

It behooved us to prove that a positive serum could not be rendered negative through the action of various indifferent bacteria, such as members of the colon typhoid group, the proteus and pyogenic bacteria. During the course of this investigation a large number of positive serums have been treated with one or more of the above-named bacteria, but invariably with a negative result.

The one question which presents itself is: Are these antibodies in the blood of children the result of an active or passive immunity? This question we have found difficult to answer satisfactorily. We recall the experiments of Ehrlich<sup>14</sup> in which he immunized mice against rizin and abrin, and later gave the young of non-immunized animals to the immune animals and *vice versa*; he found that the young of non-immune mothers would become immunized against these poisons when allowed to suck the immune animals for a time. If the same law applies to the problem we now have under consideration, we could readily explain our positive reactions on another basis than infection of the individual.

The experiments of Ehrlich show very clearly that immune bodies are excreted in the milk and that these may pass through the mucous membrane of the intestine and reach the blood. Much and Römer, in studying this phenomenon, further conclude that the penetrability of the mucous membrane of the new-born for immune bodies is by far greater than that of adults. These authors found that the source of the milk containing the immune bodies was no insignificant element. The anti-

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14. Ehrlich: Ztschr. f. Hyg., 1892, xii.

bodies contained in milk of a homologous species were absorbed much more readily than when heterologous milk was given.

Attempts were made to demonstrate the *B. abortus* antibodies in milk from cows which had recently aborted, and whose blood serum fixed the complement in high dilutions. Our results have thus far been negative, as large quantities of milk interfere with the reaction.

Attempts to deplete the milk of any eventual antibodies by treating it with an emulsion of the Bang bacillus have likewise failed to give satisfactory positive evidence that such exist in milk. It is very probable that our positive reactions were the result of an active immunity; in other words, due to antibodies generated by the individual examined. It does not necessarily follow that the positive reactions were due to an active infection of the individual. The work of Müller and others indicates that it is possible to immunize an animal by introducing the antigen per os or per rectum, provided large and repeated doses of the antigen are administered.

#### IMPORTANCE OF HUMAN SUSCEPTIBILITY

This discovery of so common a reaction in children opens up the opportunity for more study. We have first the problem as to whether this is a passive or active immunity. Then comes the question concerning the process of absorption, together with further theoretical considerations.

To the pediatricist, it is of particular interest that inoculations of guinea-pigs with the *B. abortus* has been shown to produce lesions of the lymph-nodes, spleen, liver, kidney, testicle, lung and bones, and that these lesions are suggestive, anatomically, of those of tuberculosis. These findings of competent observers together with the experience that inoculation may produce epiphyseal enlargements, and our 17 per cent. of positive reactions among children with anatomical lesions of the osseous system, most of them with clinical diagnoses of tuberculosis and rickets, indicate very clearly the need of further investigation.



AN EXPERIMENT WITH RAW AND HEATED COW'S MILK  
AND ITS LESSON. WITH COMMENTS ON  
BACILLUS ABORTUS \*

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In January, 1910, my assistant Dr. George W. Brett and I undertook an investigation on the relative value of raw, pasteurized and boiled cow's milk as a food for unweaned animals. Experimental studies on this subject commonly have one or both of two weaknesses—the use of an insufficient number of animals and an inadequate period of time during which observations are made; hence Dr. Brett and I determined to use the largest number of animals we could properly handle and keep them under observation in all cases from birth until they died or reached adult life, and in some cases after they had reached adult life, to test their vital efficiency as far as this would be measurable by the number and vigor of their progeny during one year.

The animals selected for our investigation were guinea-pigs, as they were the only species of which a sufficient number of the proper age and a definitely known history could be obtained. We realized that data derived from guinea-pigs could not be applied, off-hand, to all species of animals that are at times fed on cow's milk under artificial conditions as a substitute for mother's milk under natural conditions, but we assumed that they would have a fairly broad significance, especially as the main argument against the use of heat to destroy those disease germs with which ordinary commercial milk is too often contaminated, and which cannot be excluded unfailingly from milk that is produced with unusual precautions under exceptionally favorable conditions, is that milk contains important thermolabile enzymes and that its proteins and lime salts are modified by heat in a way that reduces their digestibility and food value.

If heat reduces the quality or the value of the milk provided by Nature for the young of cattle, it is not unreasonable to assume that this can be shown as well or better by tests with guinea-pigs, or animals that require food much like that of cattle, as with animals that are designed to digest food of a wholly different kind. The assumption, on the other hand, that cow's milk includes anything in its physical or chemical

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\* Attention is called to the paper of Larson and Sedgewick in this issue on the *Bacillus abortus*.



character, thermolabile or thermostabile, that has more value for infants than for the young of cattle or other truly vegetarian species of animals, on general biological principles, is hardly tenable, as Nature cannot reasonably be supposed to provide through the mothers of one species of animals for the needs of the progeny of another wholly unrelated and distinct species.

From one point of view guinea-pigs are not ideal animals for an investigation of the kind we made, and that is their remarkable development at birth and the short period of time during which they are dependent on their mothers for sustenance. But in this respect calves and young guinea-pigs, if we take the respective sizes and lengths of life of cattle and guinea-pigs into consideration, are much alike. Both species are born with their eyes open and their bodies well coated with hair; both are able to move about with ease on their own feet a few hours after birth, and neither has a long period during which milk is an essential article of food. Guinea-pigs are weaned when they are about 20 days old, and calves when they are from 5 to 8 weeks old. Hence, calves and guinea-pigs should be benefited more nearly alike by anything of a thermolabile character in cow's milk, or should suffer more nearly alike from changes induced in cow's milk through its exposure to heat, than calves and infants, or than calves and young animals that are less developed at birth and longer dependent on a milk diet.

The guinea-pigs used in the investigation, a total of 467 that were artificially fed on cow's milk, were removed from their mothers immediately after they were born and divided into three groups as follows:

Group 1, 155 guinea pigs, fed raw milk.

Group 2, 156 guinea pigs, fed pasteurized milk.

Group 3, 156 guinea pigs, fed boiled milk.

As this large number of new-born animals could not be secured or properly handled at one time, notwithstanding that the guinea-pig breeding stock at the Experiment Station is abundant and prolific, the actual, artificial feeding of young guinea-pigs extended over a period of ten months, from January to October, inclusive. Each time new-born animals were selected from the breeding pens they were divided into three equal lots, and one lot added to each of the three previously designated groups.

The milk for the tests was obtained from Experiment Station tuberculin-tested cows; in quality it was equal to or better than the best milk obtainable at any price in our cities, and none of it was more than eight hours old at the time it was fed to the guinea-pigs. The pasteurized milk was exposed to a temperature of 60 C. (140 F.) for twenty minutes and then rapidly cooled, and the boiled milk was slowly heated, in about

ten minutes, to the boiling point, and kept at that temperature one minute and then rapidly cooled.

During the first twenty days of their lives the guinea-pigs were fed five times daily with a special nursing apparatus, consisting of a graduated glass tube fastened to a wooden stand by means of screw clamps and communicating through a fine rubber tube with a nipple. The little animals quickly learned the use of this apparatus and showed as much affection for it as an artificially fed infant shows for its bottle.

The amount of milk given at each feeding was 1 cubic centimeter. After the twentieth day a pan of milk was accessible to the guinea-pigs for ten days longer, and then all milk was withdrawn from their diet. From the beginning the animals had access to other food than milk, and most of them began to eat small quantities when they were only a few days old.

An attempt was made to do the same work with rabbits, but the death-rate among them during the first ten days was so high that it was abandoned. Even when the young rabbits, which are born with their eyes closed and their bodies naked, were kept in a soft nest in an incubator after removal from their mothers, most of them died before they were a week old.

The difference in the value of the three kinds of milk, raw, pasteurized and boiled, was measured in two ways—by the mortality among the experimental animals and by the average weight at different periods of the animals that remained alive. The accompanying table gives the mortality record.

TABLE 1.—PERCENTAGE MORTALITY AMONG THE GUINEA-PIGS

Mortality	Young with Mothers, Per Cent.	Young Fed Artificially on Cow's Milk		
		Raw Per Cent.	Pasteurized, Per Cent.	Boiled Per Cent.
First ten days.....	4.0	27.74	30.13	27.56
First twenty days..	5.0	40.00	46.16	39.74
First thirty days...	6.0	44.52	51.28	42.95
First year .....	14.0	52.90	53.85	46.79

The first column of percentages is based on guinea-pigs that were raised by their mothers in the Experiment Station breeding pens, from which all the animals for the investigation were derived.

The enormous difference in this table between the death-rates of the guinea-pigs that remained with their mothers and those that were fed artificially on cow's milk, or the milk of a foreign species, is very impressive. The percentage death-rate for the guinea-pigs left with their

mothers is based on all the young born alive, weaklings as well as others, and no weaklings were selected for the artificial feeding tests. If we bear this in mind, the difference between the use of mother's milk under natural, and of the foreign milk under artificial, conditions will be recognized as really greater than the figures in the table show it to be.

The difference between the results with the raw, pasteurized and boiled milk are in favor of the boiled milk. During the first thirty days of life there is no well-marked difference between the raw and boiled milk, and both, unexpectedly, have a better record than the pasteurized, which latter, however, seems to have left the animals alive at the end of thirty days in such condition that a sufficient proportion of them

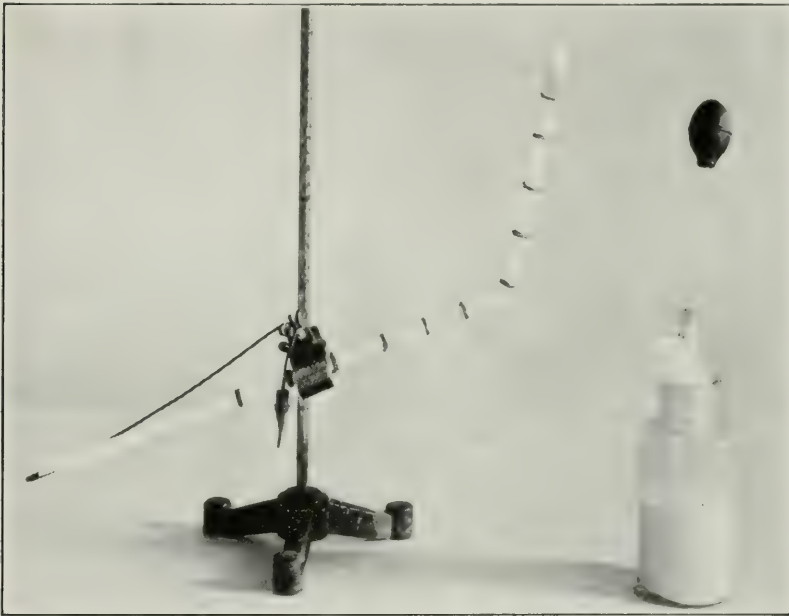


Fig. 1.—Apparatus with which young guinea-pigs were artificially fed on cow's milk.

remained alive during the following eleven months to make the records for the raw and pasteurized milk at the end of the year practically alike.

The percentage mortality table, reduced to its simplest terms, means that, in four groups of new-born guinea-pigs, each of which was composed of 156 animals, 134 of the natural group were alive at the end of the year, while of the other three groups, only 74 raw, 72 pasteurized and 83 boiled cow's milk animals survived. The natural group is 51 animals, equal to nearly one-third of the total number in each group, ahead of the boiled cow's milk group, which latter is 9 animals ahead of the raw and 11 ahead of the pasteurized cow's milk groups.

The better showing of the boiled milk must be considered with a clear appreciation of the fact that we are not dealing with ordinary commercial milk, but, on the contrary, with a milk of superlative quality.

The causes of death were mainly inflammation of the stomach and bowels and pneumonia. The post mortem examination of some of the animals that died very young revealed no satisfactory lesions to account for death.

The next table (Table 2) shows the average weight of the guinea-pigs in each group at different ages.

The first column of Table 2 is based on the average weight of 100 guinea-pigs raised under normal conditions in the Experiment Station breeding pens.

TABLE 2.—AVERAGE WEIGHT IN GRAMS OF GUINEA-PIGS AT DIFFERENT AGES

Time of Weighing	Young with Mothers	Young Fed Raw Cow's Milk	Young Fed Pasteurized Cow's Milk	Young Fed Boiled Cow's Milk
At birth .....	75.94	75.94	76.04	76.22
10th day of life.....	127.34	116.27	118.37	119.35
20th day of life.....	182.84	175.19	176.68	180.57
30th day of life.....	234.65	228.81	230.04	233.71
50th day of life.....	349.15	317.25	320.23	318.36
80th day of life.....	502.29	422.16	427.17	430.49
110th day of life.....	597.76	528.30	523.84	531.88
140th day of life.....	671.56	587.81	596.72	592.43
170th day of life.....	732.34	645.29	655.69	646.07
200th day of life.....	776.63	697.12	700.15	699.14
230th day of life.....	822.00	741.14	741.65	750.58
260th day of life.....	858.84	789.48	781.61	795.42
290th day of life.....	913.27	817.87	813.08	839.46
320th day of life.....	944.07	853.81	836.15	879.71
350th day of life.....	965.23	885.03	872.99	904.86
End of first year....	974.29	895.51	888.40	920.86

It is remarkable how nearly the average weights of the guinea-pigs in the different groups correspond on the thirtieth day, or ten days after weaning. This is partly due to the fact that the weaker and less thrifty animals in the artificially fed groups had been practically all eliminated by death before they were thirty days old, and that a much larger proportion of the weaker and less thrifty remained alive under natural conditions. After the thirtieth day the average weight in the natural group increased more rapidly than in the artificial groups, and at the end of the year shows a clear advantage of 53.5 gm. over the heaviest artificial group.

As in the mortality records, the boiled milk weight record is distinctly better than that of either the raw or the pasteurized milk, and the pasteurized drops a little behind the raw milk.



It is not fair to base conclusions on such slight differences as we have in this investigation, both as to mortality and weight, between the raw and pasteurized milk animals, else one might be inclined to infer, with the better records for the boiled milk, that the milk of a foreign species, when it is used as food for unweaned animals, contains both desirable and objectionable thermolabile elements, and that the desirable elements, which we can well afford to sacrifice to be rid of the objectionable, are



Fig. 2.—Young guinea-pig being fed artificially on cow's milk. The feeding was all done in fly-proof cages.

affected by lower degrees of heat to a greater extent than the latter. If the difference between the raw and the pasteurized milk was as great as the difference between the raw and the boiled, we would have satisfactory grounds for this inference. Incidentally, I would like to say that there are problems along this line regarding which we are very much in the dark, and that, apart from any treatment artificially used milk may require because of its contamination with pathogenic or other micro-

organisms, we have just as much evidence to support a hypothesis to the end that the milk of one species should be neutralized by heat before it is used as food for the unweaned young of another species, as to support the more commonly entertained hypothesis that the milk of one species contains thermolabile properties that are valuable for the young of another species.

From the guinea-pigs that were alive and well when they reached the age of 1 year, a number of males and females, fair representatives of each of the different groups, were selected and placed under conditions identical with those under which the Station's regular breeding stock is kept, and this gave us the data on which Table 3 is based.

The young were kept under observation until they were 30 days old, at which age there was no material difference among those from different groups of parents.

TABLE 3.—BREEDING RECORD

Guinea-Pigs Raised on	No. of Males	No. of Females	No. of Litters	No. of Young	Young Born Dead	Young Living Less Than 30 Days	Young Alive at End of 30 Days
Mother's milk . . . . .	5	15	62	210	12	11	187
Raw cow's milk . . . . .	5	15	37	120	15	6	99
Pasteurized cow's milk	5	15	52	170	15	8	147
Boiled cow's milk . . . .	5	15	52	177	11	10	156

Table 3 shows clearly that the artificial feeding of young animals on the milk of a foreign species imposes a handicap which may persist long after the milk-drinking period of life has been left behind. The naturally raised guinea-pigs show a greater productivity than the artificially raised, and again the boiled milk is more satisfactory than the raw or the pasteurized.

For the very poor record of the raw milk at this stage of the investigation, however, a fairly satisfactory explanation has been found, and this is based on the fact, discovered by Dr. W. E. Cotton and myself, that the bacillus of infectious abortion of cattle commonly occurs in the milk of infected, apparently healthy cows that produce healthy calves at full term.

While milk was being fed to our guinea-pigs it was not known that one cow in the herd that supplied the milk was infected with the abortion bacillus, and I do not see how we could have known, or discovered, or guarded against, this condition. At the time it was not known that the abortion bacillus of cattle causes peculiar, almost unmistakable lesions in guinea-pigs, which develop slowly, rarely cause death and gradually

disappear. Neither was it known that the bacillus is eliminated from the bodies of infected cows with their milk, as it had never been demonstrated to occur in milk. Cotton and I had previously discovered the lesions of abortion disease in guinea-pigs inoculated with samples of milk from the District of Columbia supply, and in guinea-pigs inoculated with milk from one Experiment Station cow that was not in contact with the healthy herd, but we did not know the cause of the lesions. It was not till sometime afterward before we isolated a bacillus from the lesions in the guinea-pigs, and another interval of time elapsed before the bacillus was positively identified as the etiological factor of infectious abortion in cattle.

The occurrence of the abortion bacillus in the milk of infected cows is now supported, not only by the evidence supplied by Cotton and myself, but also by the work of Theobald Smith and Marshall Fabyeau

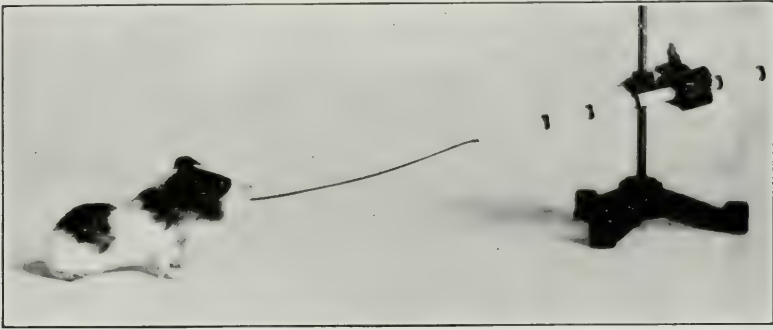


Fig. 3.—A young guinea-pig thoroughly acquainted with its artificial foster mother.

and others. In our work at the Experiment Station we have found ample reasons for believing that many, if not most, cows that become infected with the abortion bacillus remain chronic carriers for long periods of time, probably permanent carriers, and that the bacillus is of common occurrence in the milk of cows that have ceased to abort and have produced several normal, healthy calves in succession. We have records of two cows, one the mother of eight and the other of three calves, the milk of which was infected, though neither had ever aborted. Among aborting cows the bacillus appears in the milk before an abortion occurs, and in one instance was discovered in the milk of a cow that did not abort until 255 days later.

It must be clear from this that the bacillus of infectious abortion of cattle is a factor we cannot afford to omit from consideration when our choice lies between the use of raw and heated milk. We don't know as yet what effect the bacillus has on human health, but we do know, if the

general literature on the subject is reliable, that it is pathogenic for widely different species of animals, and that it is a remarkable organism because of the long time it may linger in the bodies of its hosts with undiminished virulence, and that long periods of time may elapse between its entrance into the bodies of its victims and a manifestation of the disease it causes.

Infectious abortion has become so common among cattle, and seems to be spreading so rapidly, that I have come to the conclusion that its influence on animal industry, from the strictly economic stand, is even more to be feared than that of bovine tuberculosis. In a series of milk tests made at the Experiment Station, in which 516 samples of milk from 90 dairies were injected into 1,068 guinea-pigs, 103 guinea-pigs became affected with abortion disease, and the milk distributed by 29 dairies was proved to be infected, from time to time, with abortion bacilli.

But to return to the breeding record of our guinea-pigs in the milk feeding investigation: When the guinea-pigs were killed at the end of the investigation and examined post mortem, it was found that several of those in the raw milk group showed lesions of abortion disease. Now, as abortion disease in cattle interferes somewhat with conception, it is possible that the smaller number of litters born by the raw milk guinea-pigs may have been due to the same cause, although we are not sure of this. Only one among the fifteen raw milk females used in the breeding tests showed lesions of abortion disease, and the infrequency of the disease among the guinea-pigs of the group generally indicates that the abortion bacillus did not become a factor until the milk feeding part of the tests was near its end. Young born dead were no commoner, but formed a greater proportion of the total number of young produced, among the raw than among the pasteurized milk guinea-pigs. The slightly greater productivity of the boiled than of the pasteurized milk guinea-pigs is important mainly because it gives us still another record in which boiled cow's milk is proved superior to raw and pasteurized milk as a food for young, unweaned guinea-pigs.

The first lesson the investigation teaches is, that the artificial use of the milk of a foreign species, as a food for unweaned animals, is a more lasting handicap than it is generally believed to be. The human organism is infinitely more complex than that of the guinea-pig, and may, therefore, suffer in many ways that cannot be demonstrated by tests with guinea-pigs.

The second lesson is that it is constantly becoming more and more apparent that we lack the means to produce cow's milk that is constantly free from pathogenic agents, just as the number of instances are increasing which prove that seemingly healthy individuals often are dangerous disseminators of disease germs.



The third lesson is that the time has come to ask, when a foreign milk is substituted for the milk natural to the species, whether the modifying effect of heat, irrespective of the treatment living pathogenic contaminations require, may not be beneficial rather than objectionable?

Finally, it is my sincere hope that no one will conclude from my paper that I undervalue the magnificent work of the American Association of Medical Milk Commissions. Milk is a cause of much disease, and there are several kinds of milk that are responsible for this charge. Dirty, stale, adulterated or otherwise objectionable milk, raw, pasteurized or boiled, is and remains a menace to health. Heat, applied to milk, is not a renovating, rejuvenating or a cleansing agent; all we can expect of it is to neutralize those specific germs of disease that find their way into milk, which is the best culture medium for bacteria among all articles of food, in spite of our utmost care to exclude them.

Infected milk? Unless I am greatly in error, I believe those who have studied the question impartially cannot be far from the conclusion that the infants who must, unfortunately, be fed artificially on cow's milk or the milk of a foreign species, and invalids whose diet is restricted as a whole or in part to milk, should receive properly certified milk efficiently pasteurized, or preferably, boiled, and that the general milk-supply should be made as good as the economic conditions affecting the production and handling of milk permit, and should be properly pasteurized, or preferably, boiled, under official supervision.

## THE ROENTGEN RAY IN PYLORIC OBSTRUCTION

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Much information has been gathered since the study of the stomach was begun with the Roentgen ray in conjunction with bismuth. In the adult the size, position, shape, function and presence of tumors may be ascertained with a great amount of accuracy. In the baby, however, the conclusions arrived at in the study of the adult stomach are of limited value. Some work has been done, but much more is yet to be done before the information obtainable by means of the Roentgen ray in the study of the baby's stomach will be had.

The Roentgen ray has revealed to us the erroneous impressions we have entertained, more especially regarding the position, size, shape and function of the baby's stomach. Further studies will show, among other things, the influence of the quantity, quality and composition (including the elements and reaction) of the food given on the function of the baby's stomach. The time the stomach begins to empty itself has been shown to be much earlier than was thought, and the presence of a given feeding has shown that it remains in the stomach longer than we believed. On the other hand, the Roentgen ray with the aid of bismuth corroborates our former clinical observations as to the effect of high fats in retarding the emptying of the stomach. Further study with reference to the causes which influence the various reflexes of the stomach and duodenum will be of interest in illustrating the work already done by the physiological chemist. It will be seen, therefore, that much is yet to be done in the study of the normal stomach before definite conclusions can be determined.

By closer attention to the Roentgen ray and bismuth observations in the examination of the infant's stomach, it is possible that a means of differential diagnosis will be obtained which will be of value, especially in young infants, and more particularly in conditions in which obstruction of the pylorus is suspected. It may also explain certain phenomena which make the differential diagnosis between pylorospasm and hypertrophic pyloric stenosis difficult.

While the diagnosis of pyloric obstruction is an easy one to make, it is at times difficult to differentiate between a severe pylorospasm and an hypertrophic pyloric stenosis, and when it is considered that time is a

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\* Read in the Section of Diseases of Children of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.

vital element in some instances every means to corroborate a diagnosis is essential. It is believed by some that in a marked case of pylorospasm with symptoms of loss of ground, it should be treated surgically, while others do not concur in this belief. However, if we are reasonably certain that pylorospasm is the condition under consideration, procrastination can better be practiced in the adjustment of food than in stenosis. Before arriving at any definite conclusions in the differential diagnosis by means of the Roentgen ray with the aid of bismuth in these two conditions, it will require a study of many typical cases in which absolute proof is shown either at subsequent operation or necropsy that a tumor is or is not present; and in order that these observations may be of the greatest value they should be made in some uniform way. By this I do not mean that all cases should go to operation in order to secure the information desired, but even in those cases in which the infant progresses satisfactorily much information may be obtained. Not only should the observations be made early, but also later in childhood and in after-life, in order that a better insight into the prognosis of these cases may be had.

There is no doubt that there are two distinct conditions which may cause an obstruction, namely, a pylorospasm and an hypertrophic pyloric stenosis, and that either condition may exist alone. Evidence is plentiful to show also that an hypertrophic pyloric stenosis may have associated with it spasm of the pylorus. The obstruction caused by the hypertrophic pyloric stenosis may vary, as Cautley<sup>1</sup> says, "from a degree which is fatal unless relieved surgically to a slight hyperplasia which is compatible with life."

Various theories and views have been advanced for the etiology of pylorospasm and of hypertrophic pyloric stenosis, but as these do not concern this paper a discussion of them will not be considered. Suffice it to say that pylorospasm is a functional obstruction of the pylorus, while hypertrophic pyloric stenosis is an organic obstruction due to an hypertrophy of the circular muscular layer of the pylorus, and at times also a slight thickening of the longitudinal muscular layer, with the mucosa swollen and thrown into longitudinal folds.

When the pylorospasm is severe it produces the effect of an hypertrophic pyloric stenosis, while if the hypertrophic pyloric stenosis is mild, but associated with pylorospasm, it may simulate a simple pylorospasm. The inconstancy in the severity of the symptoms in a case of hypertrophic pyloric stenosis is explained in the latter way. In pylorospasm the symptoms cease when the cause is removed, but in hypertrophic pyloric stenosis the obstruction is permanent. Since the hypertrophic pyloric stenosis is a permanent condition, and since many cases are

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1. Cautley: Brit. Med. Jour., Oct. 13, 1906, p. 939.

greatly handicapped for life by the obstruction, and since operation does not interfere with the chemism of the gastro-intestinal tract, surgical attention should be promptly given in those cases needing it.

The greatest difficulty lies, as has been said, in differentiating a severe pylorospasm from a mild hypertrophic pyloric stenosis, the reason being

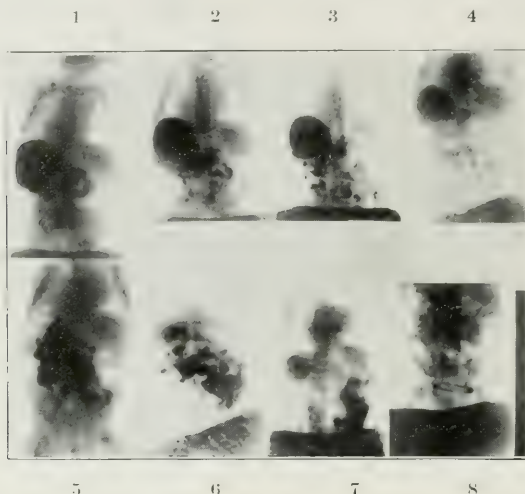


Fig. 1.—Charles. Taken immediately after giving food by gavage. In this and the following illustrations, the plate was in front, and the tube behind the patient, so that the roentgenograms are viewed postero-anteriorly.

Plate 1 (9:47½ a. m.): Note shape of the stomach and the waves. The stomach is squeezing the food out. Duodenal stream is clear, as is also stream passing through pylorus. Some food has already left the stomach.

Plate 2 (9:57½ a. m.): Note waves, also duodenal stream broken.

Plate 3 (10:07½ a. m.): Note waves. Duodenal stream visible.

Plate 4 (10:22 p. m.): Note waves. Colon can be clearly seen filled with gas.

Plate 5 (12:04 p. m.): Baby has been fed. Note that the bismuth meal is being forced out by the new feeding which appears as absence of shadow. Duodenal stream is plainly seen.

Plate 6 (2:50 p. m.): Residue in stomach. Bismuth has reached the ascending colon.

Plate 7 (5:04 p. m.): All bismuth out of small intestines and in ascending transverse and splenic flexure of colon.

Plate 8 (8:55 a. m., 23 hours after): All bismuth has been passed. Colon is outlined with gas.

the similarity of symptoms. The onset, vomiting, peristalsis, constipation and loss of weight, are found in both. A tumor may be palpated in spasm, and it may not be palpated in hypertrophic pyloric stenosis. Cumston<sup>2</sup> states that pyloric tumor was detected in only 25 per cent. of

2. Cumston: Interstate Med. Jour., April, 1911. xviii, 401.



a long list of cases studied, and Cautley<sup>3</sup> states, "I have seen cases in which the pylorus was said to be distinctly palpable and yet no hypertrophy found after death." Morse<sup>4</sup> states that "it is never safe to conclude that there is no tumor, however, unless the abdomen has been examined with the stomach, both full and empty, and with the abdominal walls relaxed, if necessary, under an anesthetic." It would seem, therefore, that some means other than the palpation of the pylorus is needed to aid in the differential diagnosis of the two conditions causing pyloric obstruction. From observations already made the Roentgen ray promises to fill the need which is so urgent. By its use we will be better able to say that this case should, and this case should not, be surgical, and it is very likely that the mortality, which is now about 50 per cent., will be greatly reduced because the babies will be referred to the surgeon before they become bad surgical risks. It is safe to prophesy that the Roentgen ray will become a routine measure, as it should be, in the diagnosis of cases of pyloric obstruction.

The ultimate outcome of cases of pyloric stenosis is variable. They must be considered from two standpoints: those operated on and those not operated on. In the first group are those who survive the operation and escape the complications which arise incident thereto, recover, and continue as healthy normal children, though the pylorus, unless a pyloroplasty is performed, remains the same, as has been shown later by autopsy (Morse-Murphy-Wohlbach<sup>5</sup>), and the food leaves the stomach through the stoma as is seen in the cases of Scudder.<sup>6</sup> I know of no instance in which it has been shown that the food leaves the stomach through the pylorus following gastro-enterostomy for complete obstruction. In other words, if the obstruction is so complete as to necessitate operation it remains so. In the second group are: (a) those borderline cases in which the patients have escaped operation, but who would have been much better off had they been operated on; they remain puny and much below par, have occasional gastric upsets, and are inclined to suffer later from gastric dilatation; (b) those patients who have had marked symptoms due to a spasm engrafted on the stenosis and who, when the spasm has subsided, convalesce and become normal children, the stenosis being only of degree; and (c) those children who may have had slight symptoms, but, under the proper care, have convalesced entirely.

With the modern appliances it is not necessary to anesthetize the child for radiographs, as instantaneous pictures can be made; and when it is necessary, an intensifying screen may be used. The observations

3. Cautley: *Brit. Jour. Child. Dis.*, May, 1908. Reprint.

4. Morse: *AM. JOUR. DIS. CHILD.*, May, 1911, i, 373.

5. Morse-Murphy-Wohlbach: *Boston Med. and Surg. Jour.*, 1908, clviii, 480.

6. Scudder: *Surg., Gyn. and Obst.*, 1910, xxi, 275.

should be made under as nearly normal conditions as possible. The meal should be at the regular feeding hour and consist of, besides the usual food, a quantity of subcarbonate of bismuth equal to 10 per cent. of the quantity of the meal. If the baby is breast-fed the milk should be withdrawn from the breast, the bismuth mixed with it, and, as in the artificially-fed baby, it should be given by gavage. In this way observations can be made immediately after feeding. If the average capacity of the stomach for the different ages is remembered, and the size of the

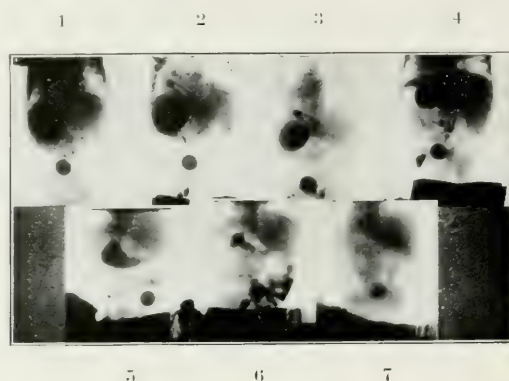


Fig. 2.—Amelia.

Plate 1 (11:16 a. m.): Note waves. Retort shape stomach. Peculiar circle at pylorus. Some food (bismuth) has left the stomach.

Plate 2 (11:26 a. m.): Note waves. Very small quantity of bismuth has left the stomach. Note fine duodenal stream.

Plate 3 (11:35 a. m.): Very little has left the stomach. Note waves are well marked.

Plate 4 (12:15 p. m.): Note waves. Shadow still to left of median line.

Plate 5 (1:03 p. m.): Stomach has become relaxed and assumed transverse position. Baby is turned a little, which may give opportunity for faulty reading of plate as to position.

Plate 6 (3:05 p. m.): Bismuth still in stomach. Gas in stomach marked. Bismuth in cecum and ascending colon.

Plate 7 (9:10 a. m., twenty-two hours later): Bismuth expelled from bowel. Gas in stomach well marked. Outline of colon well seen.

meal made accordingly, the stomach will not be overdistended and the picture will appear as under normal circumstances. The bismuth does not affect the function of either the stomach or the bowels, and I have found that the number of stools per day was neither increased nor decreased.

The position in which the baby is to be placed may be either vertical or horizontal. While the vertical position may give better information because of bringing the viscera covered by the liver more into view,

observations made on young infants in this position are made under abnormal conditions. In the prone position the baby may be placed on his abdomen or on his back. Observations in the former position will also be under abnormal conditions, but if the baby is placed in the latter position as he usually lies after feeding, the observations are more apt to be natural. Of course, it is essential that the detail should be brought out so that if it be necessary the position should be changed to obtain the best results, always endeavoring to have the conditions as nearly normal as possible.

The information to be derived from the radiographs regarding the stomach is the position, shape, size, size of flow through the pylorus when the flow begins, and the length of time required to empty the stomach completely. An absence of shadow is also significant.

The stomach occupies the left hypochondriac region and extends through the epigastric region to the right where the pylorus is overlapped by the liver. Its shape is variable as has been shown by Pisek,<sup>7</sup> and may be of the Scotch bag-pipe, tobacco-pouch, pear, or retort shape. The adult fish-hook type is found only after the second year. The position in which the observations are made may influence the shape, as is shown by comparing the radiographs of Pisek<sup>7</sup> with those of Ladd.<sup>8</sup> The stomach contracts in a particular manner in the normal infant stomach: instead of the peristalsis which is seen in the adult, the stomach contracts in all directions in a squeezing manner. Nature seems to provide against any injury to the stomach by having an air space which acts in a pneumatic way. It is possible that its presence may be the explanation of the projectile vomiting of the baby when there is an obstruction at the pylorus. The size of the stomach varies according to age under normal conditions, and it may be seen dilated or contracted under abnormal conditions.

The rapidity with which the food leaves the stomach is surprising: frequently by the time a meal is finished and an exposure made, some food has already escaped from the stomach. Position of the body does not seem to affect it. It is not always possible to determine the size of the flow through the pylorus, probably because the flow of food is not continuous. The food remains in the duodenum only a short time, passing through spasmodically so that the duodenal stage may also be missed. The length of time required for the stomach to become completely empty has been shown to be variable. Leven and Barret,<sup>9</sup> in a large number of infants from 2 to 6 months old, found the time to

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7. Pisek: *Trans. Am. Ped. Soc.*, 1913.

8. Ladd: *Trans. Am. Ped. Soc.*, Washington, May 9, 1913.

9. Leven and Barret: *Radioscopie Gastrique et Maladies de l'Estomac*, 1909, p. 173.

vary between one and three-quarter hours to two hours for both woman's and cow's milk. Pisek<sup>7</sup> believes the probable emptying time to be less than three hours, and the average final emptying time to be three hours. There are many factors to be considered, however, which influence the emptying time of the stomach. Ladd<sup>10</sup> states that the stomach appears to empty itself of the greater part of its contents from one and one-half to two and one-half hours and that the residue is emptied very slowly.

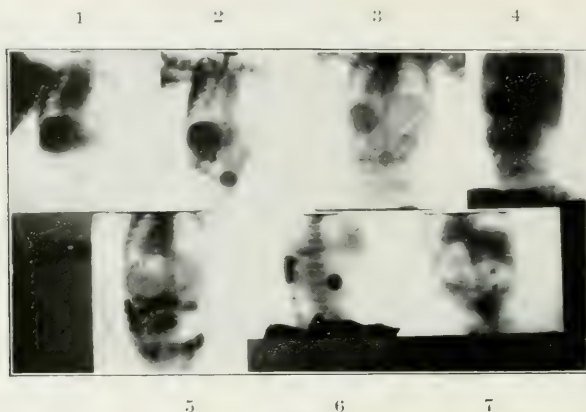


Fig. 3.—Lilian.

Plate 1 (10:10 a. m.): Note stomach in transverse position. Evidence of waves. Nothing has passed into intestines.

Plate 2 (10:15 a. m.): Note hour-glass appearance of stomach. Ball of bismuth being expelled. Gas probably intermingled with bismuth. Bismuth in small intestine.

Plate 3 (10:25 a. m.): Note waves. Hour-glass shape of stomach. Ball of bismuth being expelled.

Plate 4 (10:38 a. m.): Note four waves forcing forward balls of bismuth.

Plate 5 (12:33 p. m.): Bismuth in ascending, transverse and descending colon. Gas in stomach well marked. All bismuth out of stomach.

Plate 6 (3:00 p. m.): Gas marked in ascending and transverse colon. Bismuth in descending colon. Gas in stomach well marked.

Plate 7 (8:50 a. m., 23 hours later): Stomach outlined with gas.

often after remaining for four, five or even seven and one-half hours in both breast-fed and bottle-fed babies. An interesting point is that the residue from the bismuth meal does not appear to mix with a subsequent meal given three hours afterward. Experiments of Ladd<sup>11</sup> show that high fat, fat-free milk and milk with a high protein content retard the emptying of the stomach.

10. Ladd: AM. JOUR. DIS. CHILD., 1913, v, 349.

11. Ladd: AM. JOUR. DIS. CHILD., 1913, v, 357.



In obstruction of the pylorus the radiographs show that the shadows are frequently different from those of the normal stomach in size, shape and position, but more particularly the serial radiographs show the greatest differences to be in the function of the stomach. Observations recorded have been very few, but from the study of them the following may be said: In spasm the shape may not be altered, and in stenosis also the stomach may not be altered in shape, but at times it appears as a round ball (Murphy<sup>12</sup>); both conditions may give the characteristic waves of obstruction; in spasm the position may be the same as in the normal stomach, but in stenosis the shadow of the stomach is frequently limited to the left side and there is no shadow in the pylorus or duodenum; if the stenosis is not complete the stomach will appear as in spasm; the function of the stomach in spasm is changed in a degree, that is, the food may be slower in beginning to leave the stomach and the stomach is emptied spasmodically; it also may require a little longer time for the stomach to empty, whereas in stenosis the food leaves the stomach extremely slowly in some cases and not at all in others, depending on the degree of the stenosis. In Ladd's<sup>13</sup> case a very small quantity of the bismuth was seen in the intestine in two hours, and in Scudder's<sup>14</sup> case no bismuth had left the stomach in four hours.

In only three of four cases coming under my observation during the past ten months have I been able to obtain radiographs. While the number is small I believe that each case is of sufficient interest to report.

#### CASE REPORTS

CASE 1.—Charles was born on Sept. 9, 1913, sixteen days before he was expected, and was delivered by abdominal cesarean operation. He weighed 7 pounds 10/16 ounce. He was seen by me on the day of his birth. The family history was negative, with the exception of a miscarriage due to a fall. The first day the baby was given water, which he vomited. On the second day he was given 1 ounce of a 6 per cent. sugar of milk solution at two-hour intervals, which he vomited at times. On the third day he was put to the breast. He frequently vomited the breast milk. As the mother had very little milk and the baby was losing weight, a complemental feeding consisting of a 1 per cent. fat, 7 per cent. sugar, .90 per cent. protein and 6 per cent. alkalinity was given. The baby did not seem to care for his food and at times refused to take it. His first yellow stool was passed on the eighth day. His weight at this time was 6 pounds 14 ounces. Not knowing just what he was getting, observations were made to determine how much milk he obtained from his mother. By weighing him before and after nursing it was found that he would get from  $\frac{1}{4}$  to  $\frac{1}{2}$  ounce at each feeding. A sufficient quantity of the complemental feeding was given to meet his requirements. This method of feeding was pursued until the sixth month, the quantity and strength of food being increased from time to time, always approximating the capacity of the stomach. The alkalinity was lime water equal to 50 per cent. of the amount of milk and cream. From the time this was

12. Murphy: *Surgical Clinics of John B. Murphy*, 1913, ii, No. 1.

13. Ladd: *AM. JOUR. DIS. CHILD.*, 1913, v, 355.

14. Scudder: *Surg., Gyn. and Obst.*, 1910, xxi, 285.

begun he commenced gaining and at his sixth month weighed 14 pounds 6 9/10 ounces.

On September 16 typical peristaltic waves were noticed, and while the explosive type of vomiting became more pronounced, no tumor was positively palpated. From this time on the peristaltic waves and explosive vomiting became more and more characteristic. At times he would vomit over the side of the crib to a distance of 3 or 4 feet. On September 21 a crowing sound was first heard when he was nursing. It became significant later as indicating that his stomach was full, as evidenced by explosions if nursing was continued. By careful feeding, particularly as to composition, alkalinity and quantity, it was possible to minimize the number of vomiting attacks, so that he frequently would have only one a day. His weight was noticed carefully and showed a daily gain. His stools were normal, there being only one daily. The explosions continued from time to time, gradually becoming less frequent until January 18, when the last one occurred. The waves became less and less evident as the baby became fatter. A discomfort noticed after feeding when the waves were apparent, however, continued after the waves could no longer be seen.

Jan. 19, 1913, the radiographs herewith presented were made. His usual feeding of 6 ounces of a 1.5 per cent. fat, 7 per cent. carbohydrate, 1.29 per cent. protein was given, to which was added three teaspoonfuls of subcarbonate of bismuth. He was placed in a horizontal position on his back. As will be seen, his stomach is functioning nearly normally. Bismuth was found in his stool five hours after the bismuth was given him, and he had one stool as usual on that day.

At present the baby is apparently healthy and his stomach functions normally. When last seen at the age of 7½ months he was taking 8 ounces of a 3 per cent. fat, 7 per cent. carbohydrate and 2.10 per cent. protein at three-hour intervals. and a cereal jelly once daily. He weighed 16 pounds. On one or two occasions when he had some acute infection of his nasopharynx a mercurial purgation followed by castor oil was given and was well borne.

CASE 2.—Amelia was seen in the out-patient department of Touro Infirmary on Dec. 17, 1912, when she was 5 weeks old. She was born at full term and weighed 7 pounds. There was a luetic family history. She was breast-fed, but had frequently vomited since birth. Her weight when first seen was 8 pounds 4¼ ounces. Her stools were black until the third day. She was small, had a wig, the posterior bosses were prominent, and there was scaling of her palms and soles. Otherwise the examination was negative. On December 21 the Wassermann was negative. She had been having three to four green, watery stools daily. She improved slowly, vomited occasionally, and her stools improved in character and decreased in number. She was weighed before and after nursing the breast and showed a gain of only 2½ ounces. At her third month she was constipated. She vomited after, and also between, nursings. March 18 the mother reported that the baby vomited frequently, the vomiting being explosive in character. She was having three to four stools daily, and had lost weight. Her weight was then 9 pounds 8 ounces, having lost ¾ pound since February 24.

Peristaltic waves could be seen, but owing to the rigidity of the abdominal walls palpation was unsatisfactory. No tumor was felt. She got only 2 ounces at each nursing at this time. She was ordered 6 ounces of a weak mixture of a 1 per cent. fat, 7 per cent. carbohydrate, .90 per cent. protein, and 6 per cent. lime water every 2½ hours. March 25 she did not retain the food, had green stools and explosive vomiting continued.

April 5 the Wassermann was positive. The following day the mother was given 6 decigrams of salvarsan and the baby was allowed only breast milk.

April 8 radiographic observations were made. She was given 6 ounces of milk mixture with three teaspoonfuls of bismuth subcarbonate and the accompanying radiographs were taken. She was placed in the horizontal position on

her back. Bowels did not move until twenty hours after the observations were made and bismuth was found in the stool.

April 26 no explosions since mother was given salvarsan, and since inunctions of mercury were begun two weeks before. At present the baby is continuing to improve, takes all food and is much better in every way.

CASE 3.—Lilian was born Feb. 16, 1913, at term. The confinement was normal and the baby weighed 6 pounds 12 ounces. She was first seen March 4 because she was not doing well. She was breast-fed and vomited at times. She had several green, watery stools daily. She weighed 6 pounds 12 ounces. Family history was negative and physical examination showed a small baby with pinched expression, poorly nourished. Otherwise the examination was negative. She was given a complemental feeding of 2 ounces of 1 per cent. fat, 7 per cent. carbohydrate, .90 per cent. protein and 6 per cent. alkalinity.

The infant was again seen March 11 when I was called on account of the illness of her brother. Because of the baby's appearance the mother was instructed to weigh her before and after nursing in order to determine the quantity of food that the baby was getting, and to continue the complemental feeding, because she had gained only 3 ounces since March 4 and apparently was not thriving. For various reasons the observations were delayed and it was not until March 21 that she was seen again. An examination of her mother's milk showed 6 per cent. fat and specific gravity 1.030. The symptoms became more marked and on March 22 a typical explosion was seen. It was said that she had had such explosions before, the first explosion having occurred shortly after her birth. At this time she weighed 7 pounds 12¾ ounces. Peristaltic waves were seen. The breast-milk was ordered withheld for a few days in order to determine whether it was the cause of the vomiting, and the baby was given the complemental food as already ordered, except that 4 ounces were given instead of 2 ounces, with lime-water equal to 50 per cent. of the amount of milk and cream, every two hours. She began gaining, though very slowly, and on March 31 weighed 8 pounds 13/8 ounces. The symptoms continued and became more marked, there were frequent explosions, and peristaltic waves were constantly seen during and after feeding. Her bowels moved six times daily; stools well digested but soft. The mother had allowed her breasts to stop secreting milk. A wet-nurse was considered, but because of the radiographic findings and the gain in the baby's weight artificial food was resorted to exclusively. A satisfactory palpation of a tumor was obtained.

On April 6 she was given 3 1/3 ounces of her regular formula (which was at the time a 1.33 per cent. fat, 7 per cent. carbohydrate, 1.20 per cent. protein, 17 per cent. lime-water), with two and one-half teaspoonfuls subcarbonate of bismuth. The radiographs herewith presented were then made. She was placed in a horizontal position on her back. Bismuth was found in the stools three hours after it was given. She had six stools, as usual, the day of the observations.

At present she is progressing very satisfactorily, having gained 1 pound 8½ ounces in the previous twenty-two days. The last explosion occurred on June 1, but waves can be seen during and after each bottle. The cinematograph pictures were made June 12, 1913. She is now taking 5 ounces of a 1.80 per cent. fat, 22.5 per cent. carbohydrate and 1.8 per cent. protein at each feeding, and is having two perfect stools daily.

#### DISCUSSION

Early in the case of Charles (Case 1) I was inclined toward the belief that he had a congenital hypertrophic pyloric stenosis because of the history, the promptness with which the symptoms began, the constipation, the projectile vomiting and the peristaltic waves. The loss of weight during the first three days was not extreme, but I believed that it was due to having begun promptly with the feeding. The inability to



palpate the tumor may have been due to the fact that there had not been much wasting with the consequent thinning of the abdominal walls, making palpation more satisfactory. However, realizing the infrequency of palpating the tumor, failure to find it was not considered unusual. The slow gain in weight may have been found in other conditions. At 1 month the baby weighed 8 pounds, or  $8\frac{1}{4}$  ounces more than at birth, which was believed to be satisfactory considering existing conditions. As the baby improved, the symptoms becoming less marked (though they persisted); the possibility of a pylorospasm being the cause of the symptoms was not lost sight of. On January 19, though the baby was progressing particularly well, it was decided to determine the function of the stomach. The evidence obtained led me to believe that the symptoms may have been due in great part to spasm of the pylorus because of the excellent functioning of the stomach; but the continuation of peristaltic waves and the prolonged stay of the bismuth in the stomach (more than five hours) were sufficient to warrant a diagnosis of hypertrophic pyloric stenosis a degree with probable spasm.

In the case of Amelia (Case 2) the feeding, vomiting and stools would suggest a digestive disturbance, but the projectile vomiting and peristaltic waves, with the other symptoms, would indicate a pylorospasm. However, the luetic condition may have played an important rôle in this case. The slowness with which the food left the stomach, the length of time it remained in the stomach, and the waves suggest an obstruction of the pylorus. The fine duodenal stream may also be indicative of some obstruction. The peculiar circle in the region of the pylorus and duodenum may be significant. The radiographs shown in this case, the symptoms, family history, personal history, and the amelioration of the symptoms coincident with the beginning of antiluetic treatment (the baby taking food after, which before the treatment she could not take), strongly point to the luetic condition as being an influencing factor at least in producing the obstruction (probably pylorospasm) which was the cause of the symptoms in this case.

In Lilian's case (Case 3) the condition is one more especially of pylorospasm though there may be a degree of hypertrophic pyloric stenosis. The onset of the symptoms, the characteristic vomiting and peristaltic waves are indicative of some obstruction. The frequent stools would suggest a spasm, but the presence of a palpable tumor, while it may be rarely felt in spasm, is more suggestive of an hypertrophic pyloric stenosis. However, with the evidence obtained with the Roentgen ray, the position of the stomach, the early outflow of bismuth and emptying of the stomach, the condition is undoubtedly due in a great measure at least to pylorospasm.

I wish to express my thanks to Dr. E. C. Samuel for the radiographs presented in this paper.

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## VULVOVAGINITIS IN CHILDREN \*

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A striking change has been evident in hospital and medical practice within the last ten years. The advent of social service work in the hospital routine has resulted in a new conception of many disease conditions. Certain diseases have been long recognized as intimately connected with conditions of living, and steps have been taken toward the prevention of such diseases and the protection of the community from the spreading of the infection. Tuberculosis stands as a notable example of this group. Other diseases until recently considered as presenting almost entirely medical problems, are now recognized as having a large social element. As yet sufficient attention has not been given to a study of the social aspect of these diseases. Vulvovaginitis in children belongs in this class. This disease is confined largely to hospital practice, which would at once suggest that it is dependent in part, at least, on poor social conditions. In the Children's Medical Out-Patient Department of the Massachusetts General Hospital we have been studying these cases from the social as well as the medical point of view.

### CLASSIFICATION

The ordinary classifications<sup>1</sup> of vulvovaginitis in children recognize a non-specific vaginal discharge associated with certain infectious diseases, or with local inflammatory processes, such as herpes and impetigo. Such cases are not considered here. Another group includes certain vulvovaginal infections in which the etiologic organism appears to be some other bacterium than the gonococcus. A few such cases have been noted in our clinic. The exact bacterial etiologic factor in these cases undoubtedly varies in different individuals. Genito-urinary surgeons recognize certain cases of urethritis in the male which show profuse creamy discharge and are very resistant to treatment, and in which an organism morphologically similar to the gonococcus—the micrococcus catarrhalis—is found. Two of our cases were probably in this group. The third group of cases of vulvovaginitis includes those of true gonorrheal infection. Thirty of these cases have been studied.

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\*Read in the Section on Diseases of Children of the American Medical Association, at the Sixty-Fourth Annual Session, held at Minneapolis, June, 1913.

\* From the Children's Medical Department, Massachusetts General Hospital.

1. Rotch, Holt, Kerley, Koplik and others: Text-Books on Pediatrics.

## DIAGNOSIS

The diagnosis of gonorrheal vulvovaginitis is usually made from the finding of morphologically typical gonococci in a stained smear from the vagina. This is open to a possibility of error in certain cases, in that other organisms may simulate closely in appearance the gonococcus. A more definite diagnosis can be made by the means of cultures. The isolation of the gonococcus in pure cultures establishes the diagnosis beyond question of a doubt. The gonococcus is not an easy organism to cultivate. The complement fixation test<sup>2</sup> is now used extensively as another means of diagnosing gonorrhea infections. Broadly speaking, the fixation test is like the Wassermann reaction and is specific for the gonococcus. Although there are at present certain atypical reactions not perfectly understood, in general the test furnishes a reliable means of diagnosis and in conjunction with the other tests of smear and culture it is of distinct assistance in doubtful cases. We have confirmed our diagnosis in nine cases by this means.

## SOURCE

The problem of determining the source from which these children acquire their infection presents a real difficulty. Hospital and school epidemics have been recognized and studied for many years.<sup>3</sup> Fortunately at the present time such epidemics are less frequent than formerly. In these epidemics we are dealing with a known source of infection and have to discover the method of communication from one patient to another within a given institution. This is quite a different matter from determining the source of infection in individual patients who present themselves for treatment in an out-patient clinic. Much difficulty has been encountered in tracing the etiology of these infections. In a report of 344 cases, Hamilton<sup>4</sup> had 45 per cent. of the cases with undetermined sources of infection; and Spaulding,<sup>5</sup> in 83 cases, could not find the cause in 40 per cent. In thirty cases we have been able to determine a possible source for the infection in all but five cases, or 16.6 per cent. In one of these undetermined cases the patient came to the clinic only three

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2. Müller: *Wien. klin. Wchnschr.*, 1906, xix, 894; Watabiki: *Jour. Infect. Dis.*, 1910, vii, 159; Schwartz and McNeil: *Am. Jour. Med. Sc.*, 1911, cxli, 693; O'Neil: *Boston Med. and Surg. Jour.*, 1912, clxvii, 464; Smith, G. G.: *AM JOUR. DIS. CHILD.*, 1913, v, 313; Rockwood: *Cleveland Med. Jour.*, 1913, xii, 1.

3. Abt: *Jour. Am. Med. Assn.*, 1893, xxxi, 1474; Baer: *Jour. Infect. Dis.*, 1904, i, 313; Holt: *New York Med. Jour.*, 1905, lxxxii, 521 and 589; Sheffield: *Med. Rec.*, New York, 1907, lxxi, 767; Hamilton: *Jour. Infect. Dis.*, 1908, v, 133; Butler: *Interstate Med. Jour.*, 1910, xvii, 510; Wile: *Jour. Am. Med. Assn.*, 1910, lv, 1473; *New York Med. Jour.*, 1910, xcii, 501.

4. Hamilton, W.: *Jour. Am. Med. Assn.*, 1910, liv, 1196.

5. Spaulding: *AM. JOUR. DIS. CHILD.*, 1913, v, 248.

times and was not thoroughly investigated. One gave a history of using a dirty railroad toilet just prior to the appearance of the discharge. One is feeble-minded. In the other two patients no reasonable explanation for the infection could be found. Four gave a history of assault. One was infected in a hospital. In sixteen cases other members of the same family or persons living in the same house were known to be infected. Four cases were of children who contracted the disease from girl playmates. Twenty-one cases, or 70 per cent., were from preventable sources.

## SOURCES OF INFECTION

Undetermined .....	5—16.6 per cent.
Hospital infection .....	1— 3.3 per cent.
Playmates .....	4—13.3 per cent.
Assault .....	4—13.3 per cent.
Other members of family infected.....	16—53.3 per cent.
—	
Total .....	30
Known to be preventable.....	21—70 per cent.

The statement of these causes of infection immediately suggests the social problems in connection with vulvovaginitis in children. Among the children who contracted the disease from some other member of the family, we could find no instance in which instructions had been given about the care necessary to be taken with the discharge. In many instances the infected person did not know that the disease was contagious by any other than the usual method of infection. It is quite possible that in some instances instructions had been given and the family did not choose to follow them, or did not choose to admit that instructions had been given. In any event, no care was taken to prevent spreading the disease to other members of the household.

A mother said her other children have had the same trouble and she "thinks it runs in the family." Another said an older sister of our patient contracted the disease from a man, but she allowed the two girls to sleep together. A third said she herself contracted the disease from her husband, but our patient was sleeping in the same bed with them both.

## MANNER OF INFECTION

We have not tried to determine the exact manner of infection in these children, but it is probably by direct contact,<sup>6</sup> or by the same means as has been shown to be the method in hospital epidemics, by towels, clothes or other material. Efforts made to close this channel of infection would, I think, show as favorable results here as in connection with the pre-

6. Abt: *Jour. Am. Mer. Assn.*, 1893, xxxi, 1474; Cuthbert: *Am. Jour. Obst.*, 1893, xxvii, 698; Westervelt: *New York Med. Jour.*, 1896, lxiv, 748; Schweitzer: *Indianapolis Med. Jour.*, 1910, xiii, 257.



vention of hospital epidemics. I believe that a considerable number of the infections in our children could have been prevented had proper instructions been given to the persons in the family first infected. I believe that we have a definite responsibility to the community in this connection in making the individual understand the importance of the disease with which he is infected and the necessity of preventing its spreading to other people.

The infection contracted from playmates presents another situation which demands the cooperation of a social worker. Bad habits are taught young children by those older than themselves, in some instances by those old enough to understand fully the significance of sexual matters. These habits spread by imitation from child to child. Masturbation is extremely common among the infected cases. Whether as a result of this or not, I am unable to say, but these children are many of them sexually precocious. Just how far this has gone in some instances it is impossible to know, since their precociousness makes them secretive. The usual lack of embarrassment during examination seen in a child of six has entirely disappeared in many of these children. How far we can go in remedying these conditions must remain for further study, but I am confident that as we learn more intimately the history of infected children, the less often we shall have to attribute the infection to toilets and other indefinite sources. The supervision given many children by their mothers is so inadequate that there are long periods of time when they are unprotected from the influences of evil companions. We are driven back, in both the family infections and the infections from child to child, to the necessity of educating parents in their responsibility toward their children.

Prepola was a little girl of 9 years when she first came to our clinic complaining of vaginal discharge. This discharge was proved to be a gonococcus infection. Several days later the mother brought along a small brother aged 7 years with urethral discharge, also gonorrhea. The boy's discharge had been present for some time and antedated the appearance of symptoms in the girl. We concluded, erroneously as it later proved, that the boy was probably the source of infection in the girl. After nearly two years of acquaintance with the family the girl made a confession of the whole matter to our worker. She contracted the disease by direct contact from an older girl who also taught her to masturbate. She in turn infected her smaller brother.

#### INFECTION IN FEEBLE-MINDED

How important a rôle feeble-mindedness plays in this connection I am not prepared to say, but I am sure it must be considered as a part of the problem. Feeble-minded children are very irresponsible, and apparently particularly so in sexual matters. They are often infected with gonorrhea and are ready to pass on the infection to other children. It is extremely difficult to deal with these children in their homes, and



the fact that they are a source of direct physical injury to other children makes it even more imperative that they should be removed to institutions especially adapted to their care. In five of our patients the infection is directly traceable to feeble-minded individuals, and two other patients were themselves feeble-minded.

A feeble-minded colored child under treatment elsewhere for vaginitis was the inseparable playmate of one of our patients, whose sister also was found to have a vaginal discharge. A mother, who is very low grade mentally, has one child in the state reformatory and two others coming to our clinic with a gonorrheal vaginitis.

The following family history reveals a situation as pathetic as it is serious:

The younger son of a wealthy family in Russia was sent by his parents to this country because he was "crazy." He was unable to earn a living in his own country. After he arrived here he married and became the father of two children. The older of these children, aged 9 years, is also feeble-minded, but not sufficiently so to prevent her being at large in the community. The father insists on sleeping with this child and this child is found to be infected with gonorrhea. She is perfectly familiar with sexual matters and talks freely of the practices of her circle of playmates, who are boys and girls of her own age. Her most intimate friend is a second patient of ours. The habits of the two girls are such as to make the passage of infection from one to another extremely easy. A third member of the group also has a gonorrheal vaginitis.

In this train of infections—and undoubtedly others in this neighborhood will be found to be infected—the original source of infection should have been removed from the possibility of contaminating others a long time ago. The father's moral influence as exercised through his feeble-minded daughter is quite as injurious as the physical disease which he spreads.

#### TREATMENT

Published reports<sup>5</sup> of the treatment of cases of vulvovaginitis in children have a very loud note of pessimism. I do not believe that this is justifiable from the facts. We have been able in our clinic through the cooperation of Dr. Hugh Cabot to have an almost ideal arrangement in the management of these cases. They are all retained as patients of the Children's Medical Department, and the home visiting done by our social workers. The actual mechanical treatment of the disease condition in the individual patients is done by a member of the genito-urinary department who is infinitely more experienced in the treatment of these cases than any man practicing general pediatrics.

The treatment employed varied with individual cases, but in general consisted of a cleansing douche followed by the prolonged application of silver salts. There is some difference of opinion as to what constitutes a cure. Certainly the failure to find gonococci in a single smear, or the

temporary absence of a vaginal discharge, is hardly sufficient evidence on which to base a favorable report. It seems to me unfair, however, to refuse to call a patient cured when all symptoms have disappeared and the local examination, including a smear from the depths of the vagina has been negative for a considerable period of time. If these conditions exist and the complement fixation test is also negative, I do not see how there can be any question of the cure. I do not agree with those who believe that the reappearance of the discharge necessarily means a relapse. When the original source of infection still exists and there has been no reform in the habits of the patient a reinfection may easily occur and seems to me a more likely explanation than that a relapse has taken place.

The result of treatment in our thirty patients is as follows: One died in an accident before the treatment was completed. In thirteen the outcome of treatment is undetermined because of the failure to continue attendance at the clinic, due to removal from the city or some other cause. Five of these, however, were reported cured, and have been free from symptoms for a considerable length of time, although no examination of the local condition was made in the clinic. Eight cases are still under treatment varying in duration to date from one month to two years. It is interesting to note that the patient under treatment two years contracted her infection in a hospital. Eight cases are cured. The cure has been proved by a very long period of freedom from symptoms and local irritation or discharge, and in some instances by a negative complement fixation test in addition. A detailed table of these cured cases is given below:

Case	<i>Under Treatment, Without Symptoms,</i>		<i>Blood</i>
	Months	Months	
3	10	3	Negative (culture negative)
4	7	4	No record
5	7	3	Neg.; previously positive
8	21	3	Negative
11	6	6	Neg.; previously positive
18	*	24	No record
27	5	18	Neg.; previously positive
28	1½	17	No record

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\*By family physician.

The problem of vulvovaginitis in children will demand careful study for many years, but I believe if we are to make even a beginning toward the eradication of the disease we must recognize that we are dealing not only with a medical disease, but also with a social evil, and that the medical treatment alone is only a part of what needs to be done. This means that we must establish a close cooperation with the social workers in their attempt to solve the delicate questions of venereal disease. It has been our custom in the Children's Clinic at the Massachusetts

# VAGINITIS SCHEDULE

Name ..... Age ..... S. S. D. No.....

Address ..... Nationality ..... O. P. D. No.....

Date first visit to O.P.D..... Date diagnosis .... Date referred to S. S. D.....

## I. INFORMATION OBTAINED FROM PHYSICIAN.

1. Has smear been made..... Result .....
2. Has fixation test been made..... Result .....
3. Treatment:
  - a. How often is patient to come for treatment.....
  - b. Any treatment at home.....
  - c. Kind of treatment.....
4. Local condition ..... Discharge ..... Irritation.....
5. Is patient allowed to attend school.....

## II. INTERVIEW WITH MOTHER OR ATTENDANT AT TIME REFERRED TO S. S. D.

1. Mother's interpretation of situation before explanation.....
2. Mother's explanation of source of infection.....
3. Social worker's explanation of nature of disease to mother.....
  - a. How does mother react.....
4. Home:
  - a. Other members in family..... Infected .....
  - b. Any boarders or lodgers..... Infected .....
  - c. Toilet arrangements ..... Other families using it.....
  - d. Bathing arrangements .....
  - e. Sleeping arrangements .....
5. Recreation:
  - a. How long away from mother's care during day.....
  - b. Where does patient play.....
  - c. Form of play .....
  - d. Playmates ..... Boys ..... Girls .....
  - e. Reading .....
6. Habits:
  - a. Cleanliness ..... What form .....
  - b. Hours of sleeping.....
  - c. Hours of eating .....
  - d. Typical menu ..... Candy .....
  - e. Does patient masturbate.....
7. Nature of patient:
  - a. Nervous ..... b. Irritable ..... c. Obedient .....
  - d. Confiding .... e. Diffident ..... f. How much has she  
learned of sexual matters .....
  - g. What are her attachments.....
8. Medical social worker's instructions about hygiene:
  - a. Precautions against infection of others.....
  - b. Food, bathing, etc., of patient.....
  - c. Bringing in of others in family for examination.....
9. Name of school teacher..... School nurse..... Physician.....

## III. HOME VISIT.

1. Nature of neighborhood and tenement.....
2. Personal inspection of sleeping and toilet arrangements..
3. How is mother following instructions.....
4. Is confidence of mother and patient gained.....

## IV. VISIT TO TEACHER.

1. Patient's school record .....
2. Playmates, disposition, etc., as noted by teacher.....

## V. SOURCES OF INFECTION.

1. Positive ..... Probable..... Possible.....

## VI. RESULTS OF TREATMENT.

General Hospital to refer all cases of vaginitis to a social worker. We have been particularly fortunate in our social worker. She has been able to gain the confidence of the patients and of their families, and as a result it has been possible to find the probable source of infection in a very large percentage of cases. The social records of the vaginitis cases are kept on blanks on which the important medical and social data is collected. As has been done for many years with cases of tuberculosis, we try to secure an examination of all the other members of the family, at least of all the female children. We instruct the mother or other responsible member of the family in the dangers of infection and we visit in the home to see that our suggestions are carried out. We try to make the parents appreciate their responsibility. In almost every instance, when the first infected member of the family was told the true nature of the condition and made to understand the seriousness of the infection, it was possible to obtain full cooperation to prevent further spreading of the disease. The instances in which this was not the case were among families evidently on a low intellectual plane, or among families generally irresponsible for the welfare of their children. One mother, who had been keeping an immoral house, when she understood the situation, moved to a new and clean house and is faithfully doing everything for the benefit of her child. In one instance it was necessary to secure the help of a local board of health to improve the living conditions, but the conditions were improved.

#### CONCLUSION

In conclusion, may I repeat, that it is possible to find the source of infection in the majority of cases of vaginitis in children. The outlook for cure of the individual patient is good, provided the treatment is followed. To prevent the spreading of the disease, parents must be made to realize the contagiousness of the condition and the dangers in the neighborhood to which their children are subjected, provided they are not protected during the long hours of play. The frequency with which feeble-minded children act as centers of infection gives an additional argument for their isolation. The treatment of the individual patient as she presents herself for our care remains our first duty, but if we do nothing more we can hardly expect to make much of an impression on the disease as it exists in the community.



# PROGRESS IN PEDIATRICS

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## RÉSUMÉ OF THE LITERATURE ON THE EAR

S. MAC CUEN SMITH, M.D.

PHILADELPHIA

The most notable contribution to aural literature during the past year is that of Kopetzky and Haynes on the diagnosis and treatment of otitic meningitis, and this is especially noteworthy in its relation to pediatrics from the fact that a majority of cases thus afflicted are in infancy or early childhood. If the results of Kopetzky's laboratory work are sustained by further clinical observation (of which I have no doubt), they will, in the near future, be adopted as a routine procedure for the early diagnosis of otitic meningitis. Since our chief difficulty in the past has been to make an early diagnosis, before the disease was well advanced, Kopetzky's methods of determining the presence of meningitis should mark a definite advance in the successful treatment of this most fatal of all diseases.

Kopetzky<sup>1</sup> starts his study by a rereading of many published cases of meningitis, covering the entire field of meningeal infection, studying in detail the case histories and autopsy reports, and finds that what is usually differentiated as separate and distinct forms of meningitides, each a definite entity, represent in reality a number of conditions which are fundamentally similar and to a great extent progressive in type. The so-called types vary somewhat regularly in definite relationship to the causal bacterial agent, but the result of the infection of the central nervous system by the microbic invasion produces tissue reactions which are fundamentally similar in all the types.

The author concedes the difficulty in dealing with the question at issue when presenting the argument that meningitis is to a certain extent a progressive disease, in attempting to bridge the gap between the so-called "meningitis serosa" and those meningitides which exhibit frankly purulent characteristics. He calls attention to the rather common experience which clinicians have, of observations made, of clinical pictures which logically are referable only to involvement of the meninges, and in which complete recovery takes place without other therapeutic aid except removal of foci of disease in the tympanic cavity and mastoid process. The performance of lumbar puncture in such cases generally

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1. Kopetzky, S. J.: Meningitis. Nature, Causes, Diagnosis, and Principles of Surgical Relief, *Laryngoscope*, 1912, xxii, No. 6.

presents a fluid found sterile on incubation, and with negative findings as to its cytology.

Kopetzky contrasts the clinical picture and the findings in the spinal fluid in this group of cases, with the clinical picture and laboratory findings from cases of meningitides which so often follow an infectious invasion of the labyrinthine channels of the internal ear — the so-called fulminating type of otitic meningitis — and he comments on the similarity of the findings in the two classes of cases. He reasons that in the so-called fulminating type of meningitis, the lethal outcome is established before frankly purulent characteristics are evident. The fatal outcome is due to paralysis of the vasomotor, the respiratory and the vagus centers in the medulla. On the other hand, in the usual course of the so-called "meningitis serosa," the disease is either aborted through operative measures on the primary foci of disease in the adnexa of the ear, or the case eventually develops the well-known laboratory findings of purulent meningitis. In line with the more recent observations of Körner, the author holds that the serous type of meningitis is, therefore, but the initial stage of what may become a purulent meningitis, and he points out that all of the purulent meningitides pass through this stage, although in the latter instance they are unrecognized clinically. The fulminating type of meningeal infection presents the initial stage, with such a predominance of symptoms from the vagus, the vasomotor and the respiratory centers that the symptoms from the vital centers overcloud the whole picture, and the factors to which he refers are overlooked. Tracing this hypothesis further, case histories and autopsy reports are presented, taken from reliable observers, from published literature, all of which tend to show that the reports of cases descriptive of so-called distinct types of meningitides are, in reality, reports of one and the same tissue reaction studied during a different stage of its development.

Having established the progressive nature of meningeal infections, the author devotes himself almost exclusively to common factors. These common factors are the symptoms of the disease, and the analysis of the symptom-complex of meningitis — keeping in mind only the elements which produce symptoms — resolves itself into a study of the tissue reactions which result from the invasion of the central nervous system by pathogenic micro-organisms. This study of the tissue reactions, besides throwing considerable light on the causes underlying the chemical and other changes found in the cerebrospinal fluid obtained by lumbar puncture from cases of meningitides, presents valuable data, useful in establishing an earlier diagnosis of meningitis than is possible from the means heretofore at our command.

The author first studied the factors presented by brain compression, comparing these with the results obtained by artificially infecting the

meninges. Compression of the brain by increasing the endocranial tension of the cerebrospinal fluid, whether this tension results from hydrostatic means or by bacterial invasion, is the same. It results in a compressed blood-supply. The experiments of Araki, the analyses of Hoppe-Seyler, the observations of Zillesu, and the work of Martin H. Fischer, all point out that the lack of oxygenation of a part, a muscle or an organ results in acid formation. Kopetzky is satisfied that under these conditions, in cases of meningitides, where pressure factors dominate the clinical picture, the cerebrospinal fluid will give evidence of this lack of oxygenation by evidencing a condition of acidity, and the tissues a condition of acidosis.

The observations of Andrew Connell, who remarked on the presence of a "lessened alkalinity" in similar conditions, are of moment. The author advises that the determination of the reaction of the fluid must be made immediately after the withdrawal from the body, for the autolytic changes which the fluid undergoes tend to make it alkaline. This characteristic of the spinal fluid is not specific to fluids from meningitides, however, for the author gives a table showing analyses of fluids obtained from patients suffering from other diseases which produce disturbed intracranial tension, and these likewise present a degree of acidity. The acidity is of the nature termed in chemistry "combined acidity."

The lack of oxygenation is held partly responsible for the finding of lactic acid in the cerebrospinal fluid in meningitides and other diseases which produce a compressed blood-supply in the cranial cavity. The Uffelmann reagent is employed in testing for this acid.

The author then proceeds with the study of bacterial activity in the tissues of the central nervous system. He alludes to the fundamental work of Theobald Smith, Arthur Kendall, Lyons and Cramer, Dryfus, Nashimura and many others who have demonstrated that the activity of the bacteria is directly influenced by the presence in the media of their growth of available carbohydrate. The well-established finding that toxins are not produced in the presence of carbohydrate is restated, and then Kopetzky draws attention to the fact that the normal cerebrospinal fluid contains a carbohydrate now generally accepted as a form of non-fermentable dextrose. This constituent of the normal cerebrospinal fluid is the first element to be attracted by the bacterial invasion of the central nervous system, the microbial flora which constitutes the usual infective agent being of that type of micro-organism which prefers carbohydrate to protein in its dietary. Therefore, the first evidence of pathogenic microbial invasion is offered by an absence of this copper-reducing body from the cerebrospinal fluid. There are a few negligible instances where this general statement does not hold true, the most important of which



is the tuberculous infection of slow development. In all other types of meningeal infection, Kopetzky has noted the absence of the copper-reducing body from the spinal fluid obtained from cases of meningitides.

This finding is shown to precede the demonstration of bacteria in the fluid by hours and sometimes even days, and is held to be of great diagnostic value. It absolutely differentiates, according to the author, between any actual infection of the meninges, excepting the slowly-developing tuberculous type, and cases of meningism, meningeal symptoms from sepsis, and other general diseases which present meningeal symptoms during their onset or course. Furthermore, due to factors which the author details, the reappearance of the copper-reducing body later in the course of the disease has always been accompanied by the recovery of the patient, and hence he points out the value of this observation as an aid toward making a prognosis in the case. For the purpose of testing the fluid for the presence or absence of the copper-reducing body, the author recommends the employment of the Benedict solution.<sup>2</sup>

The chief and largest part of the nervous system of man consists in the so-called myelin substances, among which lecithin is the best-known prototype. The decomposition products of lecithin are then studied in the laboratory and compared with the products of this element found in the spinal fluid. Cholin, a poisonous base, is demonstrable in the fluid in larger quantities than is found in what is termed the normal minimum amount. Here the findings of Kopetzky coincide with those published by Gumprecht, Gulewitch, Halliburton and others. Finally, as an end-product, the author found a neutral fat in small percentages. In cases which terminated fatally, this always reached 1 per cent. plus.

Kopetzky concludes this section of his work by emphasizing the necessity of a complete examination of the spinal fluid to get the necessary data for exact diagnosis, and he calls attention to the determination of the so-called "meningeal index" by a method devised by Mayerhofer<sup>3</sup> of Berlin as having been found to be of distinct value.

The examination of the fluid should entail a determination of the pressure under which it is obtained, its physical, cytological and chemical constituents, and finally, its bacterial contents. Kopetzky insists that the chemical examination gives the quickest answer and permits a diagnosis of meningitis before the microbic flora of the spinal fluid is demonstrable.

There are other factors studied; for instance, the influence of the resultant stasis in the circulation of the cerebrospinal fluid, and its effect in permitting the accumulation of the products of cerebral metabolism,

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2. Benedict, S. R.: *Jour. Am. Med. Assn.*, 1911, lvii, 1193.

3. Mayerhofer: *Berl. klin. Wehnschr.*, May 5, 1913.



to add to the poisoning of the nerve centers in the cortex; also, the changed consistency in the tissues of the Pacchionian bodies, which hinder the free flow of the fluid to the venous blood-system. These, and the experiments on pure colloid (fibrin) using the normal and abnormal cerebrospinal fluid as media to test out the production of edema, as well as a detailed study of the specific gravity of the fluids in health and disease, form interesting by-problems on which light is shed.

The author summarizes, dividing the symptoms of meningitis into two divisions:

1. Those dependent on increased intracranial pressure.
2. Those dependent on the growth of bacteria, and on the decomposition products thrown into the circulation from the disintegration of nerve tissues.

Kopetzky insists that heretofore we have limited our therapeutic endeavors to combat the disease too much to efforts directed against the bacterial infection and have not made sufficient effort to lessen the intracranial tension, on the one hand, and to neutralize the chemical products of abnormal tissue functionation on the other. He contends that once the pressure factors are in hand, then the added forces which may be brought to bear on the infection itself, in the form of antitoxins, vaccines and chemical agents, will have increased value in the treatment of the symptoms referable to his second division of the symptomatology.

#### DRAINAGE IN MENINGITIS

For the control of the pressure factors, which manifest themselves clinically by an increasing blood-pressure, by the presence of swelling of an optic disk — not choked disk — and tension under which the cerebrospinal fluid is obtained, Dr. Irving S. Haynes<sup>4</sup> has devised an operation for drainage through the great subarachnoid space known as the cisterna magna, which lies close beneath the occipital bone, accessible to surgical procedure.

When under pressure, the brain is crowded against the skull, and any drain introduced between these two structures is pressed on by the former and quickly walled off by plastic lymph, and so becomes useless. The single exception to this intracranial condition and inevitable result is found at the space between the two poles of the cerebellum and between them and the medulla. This space is the cerebello-medullary angle or hiatus. It forms a large part of the great subarachnoid space known as the cisterna magna. This space is in free communication with all the other subarachnoid spaces about the brain and cord, and also, through a

4. Haynes, I. S.: *The Surgical Treatment of Meningitis — Its Scope and Accomplishment*, *Laryngoscope*, 1912, xxii. No. 6; *Trans. Ninth Otol. Congress*, 1912, p. 355.

funnel-shaped opening known as the foramen of Magendie, with the ventricles of the brain. The cerebrospinal fluid is secreted by the chorioid plexuses of the ventricles and flows from them into the great cistern before taking its final course over the convexity of the brain to enter the sinuses. It is in this region that the infected fluid first gathers, and here the effects of inflammatory activity are most marked. Haynes has shown that the skull may be opened here, even in the presence of great intracranial pressure, without the occurrence of a hernia cerebelli, and that drainage here is free and continuous, because the drainage wick leads from a natural cavity and there are no surfaces to crowd together about it, as exists everywhere else over the brain surface; furthermore, the drain will not be isolated by adhesions, because it lies in a space through which fluid is continually flowing by way of the drain to the surface.

Dr. Haynes summarizes the purposes of his operation as follows:

1. To open the cisterna magna, relieve intracranial pressure and restore the normal supply of blood to the vital centers.

2. To accomplish this without danger of cerebellar hernia or of "corking up the foramen magnum by downward displacement of the brain stem."

3. To prevent shock and possible death of the patient from too sudden escape of the cerebrospinal fluid.

4. To provide for free and continuous drainage of the infected cerebrospinal fluid and thus enable Nature to effect a cure of the disease.

5. To afford inspection of the foramen of Magendie and, if it is closed, allow of its reopening.

6. To forestall possible complications, especially hydrocephalus. Should hydrocephalus be present, its relief and cure may be possible by this operation.

7. To accomplish these desirable ends by an operation of the simplest technic, in the minimum of time, and with the least shock.

Both Dr. Haynes and Dr. Kopetzky insist that the result of the operation will depend on its *immediately* following the *early* diagnosis made possible by the latter's laboratory researches.

#### TREATMENT

The treatment of meningitis by means of an injection of hexamethylenamin into the spinal column is reported to have given excellent results in some hands, while in others it has absolutely failed and is consequently condemned. For certain reasons the procedure has always seemed to be questionable. As to its efficiency, my own experience makes me very pessimistic. In any event, the result must depend solely on the elimina-

tion of free formaldehyd, and this can only be attained under certain conditions and methods of administration, as shown by the laboratory observations of Kopetzky. I am indebted to Dr. Kopetzky for furnishing me with the results of his recent original observations on the use of hexamethylenamin [urotropin] in the treatment of meningitis. He says:

Urotropin itself possesses but small bactericidal properties. Its effects are only produced when it breaks up into free formaldehyd, and this happens most easily when the chemical reaction takes place in an acid medium. My own work has demonstrated, at least to my satisfaction, that in a certain number of cases acidosis is present in the central nervous system, and a low degree of acidity is presented in the spinal fluids of these patients. The meningitides in which this finding usually occurs are those in which evidences of an increased intracranial tension are most marked. This will probably explain the differing results obtained by one and the same man in a series of meningitides, for all do not exhibit pressure factors.

Urotropin given by way of the stomach is found as urotropin and not as formaldehyd in the blood. It is rapidly excreted in the urine both as urotropin and as free formaldehyd. It breaks up into formaldehyd and other products when passing through secretion-producing cells (epithelial cells of the type found in glands which functionate to produce secretions). The uselessness of directly injecting urotropin into the spinal canal is, therefore, clear. In introducing any product into the spinal canal, many factors must be considered. The fluid normally is a watery, clear liquid with a specific gravity of from 1.005 to 1.007, varying individually. Its salt content is very low and is of the natrium variety. Protein elements are also very low. It would seem as if the physiologic function of passing easily through the Pacchionian tissue and seeping into the venous blood channels necessitated this composition of the fluid. To add a dose of urotropin, 40 to 50 grains, even diluted with sterile water or physiologic salt solution, as I have seen done, is certainly not tending toward the establishment of normal relationship of this fluid to that of the blood plasma with which it is its destiny to mix. In many cases the clinicians employing such a procedure have simply added another factor—an irritant factor, overlooked because of the patient's condition—to the stasis in the circulation of the cerebrospinal fluid which is already present because of the edema of the meninges, including the Pacchionian bodies.

The only secreting epithelial cellular elements within the cranial vault, as far as present-day knowledge of brain metabolism goes, are the cells of the chorioid plexus, and as is seen from the evidence presented from the injection of salvarsan in the treatment of brain syphilis, these cells secrete so little of the salvarsan that a distinct disproportion is demonstrable between the amount found in the blood-stream and the quantity found in the cerebrospinal fluid two hours after the salvarsan injection. (See Rockefeller Institute reports.) These cells of the chorioid plexus, whose function it is to secrete the spinal fluid, must possess an inhibitory action on the secretion of solid matter, whether of basic salt nature or loosely combined protein elements. This must be so to preserve the spinal fluid in its normal density and composition in the face of drugs and diet whose elements are often found in the blood and not in the spinal fluid.

Finally, to force the secretion of the decomposition products of urotropin brought to the cells of the chorioid plexus by the blood, this vehicle must be surcharged with the drug, and in the face of its rapid elimination by the kidneys, this presupposes the employment of a very large dose by way of the stomach.

From experimental work not yet published, I feel that urotropin (hexamethylenamin) offers us the best means of combating bacterial activity when given in large doses, by way of the stomach, combined with cream of tartar. When pressure symptoms are presenting, the local acidosis helps the formation of the formaldehyd. Where pressure symptoms are not the predominating



factor, the large dosage causes increased secretion of the cells of the chorioid plexus.

#### DEAF-MUTISM

The ever-important question of deaf-mutism, both congenital and acquired, continues to be the subject of many communications. Notwithstanding the improved methods of teaching this unfortunate class, our best efforts must be directed to the employment of prophylaxis. In an interesting communication by MacLeod Yearsley<sup>5</sup> on the prevention of deaf-mutism, he makes the plea that all otologists should turn their attention to the study of deaf-mutism, and feels that the movement for its prevention should be international. The general practitioner generally sees the potential deaf-mute first, and on him rests the responsibility of prompt treatment and advice. Every deaf-mute school contains pupils who are the victims of lost opportunity.

Yearsley has analyzed 1,076 cases, of which 45 per cent. were born deaf and 55 per cent. acquired deafness. Of those born deaf, three groups could be arranged: (1) Those in whom no family history was obtainable; (2) those in whom family history contained no evidence of other deaf births; (3) those in whom there was a family history of congenital deafness. These really may be taken to show that there are cases of true hereditary deafness or sporadic congenital deafness. Some of the second class may have acquired deafness in very early infancy, as deafness is often not detected until the second year. Of the congenitally deaf, 145 cases in 123 families, or 24 per cent., showed deafness in direct line of parentage; 31 per cent. showed it in collateral lines; the collateral family lines are equally as, if not more important than, the direct. Out of 309 families in which there were cases of congenital deafness, cousins married in 7 per cent., and in 592 families in which there were cases of acquired deafness, cousins married in but three tenths of 1 per cent. In one school in which there was a large proportion of Jewish children, out of 137 families, consanguinity occurred in 27 per cent.; thus, combining the two percentages in the 446 families in which deaf-mutism occurred, there were 59 consanguineous marriages.

Alcohol and insanity play an important part in congenital deafness. Syphilis affected more the sporadic cases, according to Yearsley's opinion. Of the 592 acquired cases, 34 per cent. were due to the infectious diseases, 26 per cent. of these belonging to the exanthemata in the following order: Measles, 11.5 per cent.; scarlatina, 9.7 per cent.; diphtheria, 2 per cent.; influenza, 0.67 per cent.; pertussis, 1.18 per cent.; German measles, 0.33 per cent.; enteric fever, 0.33 per cent.; cerebrospinal meningitis, 0.16 per cent.; as also varicella and mumps. Of other diseases, pneumonia

5. Yearsley, MacL.: *Ann. Otol., Rhinol. and Laryngol.*, September, 1912, p. 585.



was responsible for 2.7 per cent.; tuberculosis, 0.33 per cent.; syphilis, 6.5 per cent.; diseases of the nervous system, 18.7 per cent.; and middle ear suppuration and catarrh, 20.7 per cent. Of the cases due to injury, fifty-eight of the acquired cases fell in this division.

Yearsley looks forward to laws prohibiting the marriage of deaf-mutes, blood relations, alcoholics and syphilitics; better care of children generally; more careful examination of the ears in all fevers; the recognition of the evil effects of adenoids and nasal diseases, and better teaching of otology in the medical schools.

The above résumé forcibly illustrates that, after all, preventive medicine in its relation to otology is many times the most effective, and, indeed, the only means of successful treatment. A great majority of all aural diseases and their complications start as more or less simple tympanic affections, and, if promptly treated, will frequently be arrested before any considerable damage has occurred. In other words, the correction of any abnormality in the nasopharynx, such as the removal of diseased tonsils and obstructive adenoid vegetations, and the establishment of a free nasal respiration, will prevent the extension of many pathologic processes from the same through the Eustachian tube into the middle ear. Then, again, as I have pointed out on numerous occasions, if a suppurative infection of the middle ear actually occurs, this should be promptly recognized and the fluid evacuated by an immediate incision of the membrana tympani. By the employment of these simple measures in the hands of the general practitioner, and more especially the pediatricist, most of the serious complications, such as meningitis, sinus thrombosis, brain abscess formations, and even deaf-mutism, will have been prevented.

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## INDEX TO CURRENT PEDIATRIC LITERATURE

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Lancet, London, Sept. 3 and 6, 1913.
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T. Haerle.  
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and G. A. Campbell.  
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Pylorus, Spasm and Stenosis of the, Differentiation Between.—G. Holzkecht and M. Sgalitzer.

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# American Journal of Diseases of Children

VOL. 6

DECEMBER, 1913

No. 6

## DUODENAL ULCERS IN INFANCY \*

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Until recently, duodenal ulcers have been considered rare in infancy and childhood. Since 1908, groups of cases have been published by several writers, and the increasing number of reports during the past three years indicates that the condition is not a very uncommon one, and that it has been probably overlooked in the past.

In the literature I have found references or full reports of ninety-one cases of duodenal ulcer in the first year of life, making, with four cases of my own reported in this paper, ninety-five cases for study. All but twenty-one of these have been published since 1908. These facts indicate how little this condition was known until five years ago. In the post mortem records of the Babies' Hospital embracing 1,800 autopsies, fully 90 per cent. of which were in children under 1 year, duodenal ulcer is recorded but four times, and, curiously, three of these cases were observed within a period of three months, the other case two and a half years before. It is doubtless true that had it always been carefully looked for, other cases might have been discovered.

Entz<sup>1</sup> (Budapest) reports 10 instances of duodenal ulcer in 364 autopsies on infants under 1 year, made in an infant asylum. Schmidt<sup>2</sup> (Breslau) observed 20 cases in 1,109 autopsies in infants under 1 year. A still greater frequency is indicated by the observations of Helmholtz,<sup>3</sup> who found in 16 autopsies on atrophic infants, duodenal ulcers in 8. He calls especial attention to certain superficial ulcers which may easily be missed even when autopsies are made with considerable care, since they cause no symptoms during life, and neither hemorrhage nor perforation is found at autopsy. Half his cases belong to this group. Granting that

\* Read at the annual meeting of the American Pediatric Society, Washington, D. C., May 6, 1913.

1. Entz: Közhórházi Orvostárs üléski jkoe, Budapest, Nov. 4, 1908, quoted by Flesch in *Jahrb. f. Kinderh.*, lxxvi, 542.

2. Schmidt: *Berlin Klin. Wehnschr.*, 1913, xiii, 593.

3. Helmholtz: *Deutsch. med. Wehnschr.*, 1909, p. 534; *Arch. Pediat.*, September, 1909.

there is a considerable number of such ulcers which may be detected at autopsy only with some difficulty, even then we cannot assume that duodenal ulcers in infancy are at all common. However, as compared with round peptic ulcers of the stomach they are certainly much more often seen. Thus Entz observed ten duodenal to one gastric ulcer. There is no case of peptic ulcer of the stomach in the autopsy records of the Babies' Hospital.

Of sixty-five cases in which the age of infants with duodenal ulcers is given, 70 per cent. of the patients were between 6 weeks and 5 months old, the greatest frequency being between the sixth and tenth week; only seven patients were over 5 months old; nine were in the new-born. The age incidence is very striking. It corresponds very closely with the age incidence of deaths from marasmus.

While duodenal ulcers may be seen in patients of any age and in those who are well nourished, the great majority occur in infants of the marasmus (atrophic) type. Whether there is a more definite association than simply a lowered vitality of the mucous membrane of this part of the intestine, it is impossible to say.

Two predisposing factors seem of some importance: A lowered general vitality of the patient, as in infants suffering from marasmus, and previous digestive disturbance, a history of which is present in a very large proportion of the cases.

The situation of the ulcer in the great majority of the cases is in the posterior wall of the duodenum. Practically all of them are above the papilla, and when but a single ulcer is present the usual seat is just below the pyloric ring (Fig. 2).

Of 51 cases in which the point is mentioned, there was only a single ulcer in 35 cases; two ulcers in 8 cases, and more than two in 8 cases. In size the ulcers vary from 2 or 3 mm. to 1.5 cm. in diameter. Duodenal ulcers are circular in shape, they have shelving, sharp edges, usually described as "pushed out," and often show at the base open blood-vessels of considerable size. They may involve only the mucous membrane or they may go to the muscular coat, quite to the peritoneal coat or may perforate.

Microscopical examination shows an almost complete absence of round celled infiltration and other evidences of inflammatory reaction. The mucous membrane of the duodenum elsewhere is generally normal, except that it may be blood stained. Large clots may be present in the duodenum or the small intestine lower down and blood may even be found in the colon. The stomach also may contain fresh or old blood. It is rather surprising that although gastric ulcers are believed to have the same etiology and pathology, in but a single case have I found recorded the coexistence of gastric and duodenal ulcers in the same patient, even including the cases observed in the new-born.



The association of duodenal ulcer with burns is so constantly mentioned in works on adult medicine that it is of some interest to note that not one of the recorded cases of duodenal ulcer in infants which I have collected have complicated burns. Ulcer has been found complicating many pathological conditions, but there seems to be no adequate reason for connecting it with any except marasmus, and even this is regarded by some writers as accidental.

I have nothing to add to the generally accepted view of the pathogenesis of these ulcers, viz., that they are due to thrombosis followed by self digestion of the mucous membrane over a circumscribed area. The situation of the ulcers, above the papilla, indicates that the lesion is due to the action of the gastric juice.

Below the papilla the presence of the alkaline pancreatic and hepatic secretions seems to exert a protective influence on the mucous membrane of the intestine. That it is the direct action on the intestine of the gastric juice not yet neutralized is indicated by an observation of Freund's<sup>4</sup> on an infant 2 months old, who was operated on by gastro-enterostomy for pyloric stenosis. For a time progress was favorable, then bloody stools followed by death, the autopsy showing ulceration of the jejunum below the opening which communicated with the stomach.

#### SYMPTOMS

In a little more than one-third of the recorded cases no symptoms which could be attributed to ulcer were present during life, the condition being found at autopsy in infants dying of intercurrent disease or of marasmus.

In a second group of cases death occurred suddenly in collapse, sometimes preceded by ordinary gastro-intestinal symptoms and sometimes not. In a few patients with such a history the autopsy disclosed a concealed hemorrhage, the duodenum, and in some cases the intestine lower down, containing large clots, though no bloody discharges were present during life. In other cases there was found an acute perforating ulcer and usually commencing general peritonitis. After the development of the first symptoms of collapse death may ensue in a few hours, or life may be prolonged for a day or a day and a half, rarely longer in patients of this age and class. The diagnosis of peritonitis under these conditions is extremely difficult, since neither vomiting, fever nor distention may be present, the only thing suggesting it being the acute collapse. On account of the age of the patients such symptoms as pain and localized tenderness, of much value in older subjects, are of no assistance in making the diagnosis in infants.

4. Freund: Mitt. a. d. grenzgeb. d. Med. u. Chir., xi, 326.

There is then practically only one definite symptom pointing to duodenal ulcer, viz., hemorrhage. This may appear as blood vomited or as blood in the intestinal discharges. Some idea of the relative frequency with which these symptoms occur may be gained from the following statistics: Of 64 cases of duodenal ulcer in which the clinical histories are recorded, bloody stools were noted in 28; bloody vomitus in 10; both bloody stools and bloody vomitus in 6 cases, 4 of these being in the new-born. In 2 patients there was no discharge of blood during life though the intestine at autopsy contained large blood-clots. The blood vomited may be bright, clear blood, or coffee-ground material. It is not usually in large amount, although in the new-born as much as half an ounce or an ounce has been recorded. Blood from the bowel may be in such small amount as merely to show a trace in the stool, or large clots may be passed and even fluid blood in considerable quantity. Once the hemorrhage has occurred it is apt to persist until the death of the patient, which usually comes within twenty-four or thirty-six hours from its first appearance. It is surprising how small an actual loss of blood may produce very serious symptoms in the class of patients in which most of these ulcers occur. In several cases the collapse has been so acute and so severe as to suggest perforation, though the autopsy showed only concealed intestinal hemorrhage. It is, then, the appearance of blood in the stools, usually in considerable amount, which first suggests duodenal ulcer, and in patients of the marasmus class or in young infants from 1 to 5 months old this cause of hemorrhage should always be borne in mind.

The association of duodenal ulcer with spasm of the pylorus has been too often observed to be considered accidental. In Torday's case,<sup>5</sup> an infant 8 months old, exhibited characteristic symptoms of pyloric stenosis — persistent, forcible vomiting and marked peristaltic waves — yet the autopsy showed no stenosis, but a duodenal ulcer just below the pyloric ring, with a greatly distended stomach. Ulcer of the duodenum associated with pyloric stenosis has been mentioned by Finny,<sup>6</sup> Ibrahim<sup>7</sup> and Freund,<sup>4</sup> and Birk<sup>8</sup> observed three cases associated with pyloric stenosis and one with pyloric spasm. In the above references the distinction between pylorospasm and pyloric stenosis is not always clearly made. It is easy to see how an ulcer in the duodenum just below the pyloric ring might by irritation cause pyloric spasm with symptoms closely simulating pyloric stenosis, although the latter condition was not present. It is perhaps enough in this connection to call attention to the association of these two conditions, and to emphasize the point that when symptoms

5. Torday: *Jahrb. f. Kinderh.*, 1906, lxiii, 563.

6. Finny: *Proc. Roy. Soc. Med.*, 1908-9.

7. Ibrahim: *München. Ergeb. der inn. Med. u. Kinderh.*, 1908, i, 220.

8. Birk: Referred to by Helmholtz, *Arch. Pediat.*, September, 1909.

suggesting pyloric stenosis are seen for the first time in an infant over 3 or 4 months old, duodenal ulcer should be borne in mind as a possible explanation.

Something should also be said regarding the relation of duodenal ulcer to melena, or the gastro-intestinal hemorrhages of the new-born. Dusser,<sup>9</sup> in thirty-one collected autopsies on such cases, mentions five in which the only lesion was a single duodenal ulcer; in four of these, blood was vomited as well as expelled by stool. In a patient of my own (Case 4) dying on the twelfth day, multiple erosions were found in the stomach as well as an ulcer in the duodenum. In reviewing the cases seen in the new-born one is struck by the fact that the hemorrhages were more extensive than in other cases of duodenal ulcer and seemingly out of proportion to the size of the ulcer; also that they were usually both gastric and intestinal. This gives rise to a suspicion that the cause of the bleeding in these cases is a general one and not entirely the ulcer and possibly not even connected with it. There are no sufficient reasons for invoking a different pathology for the ulcers occurring at this time of life and those which are seen in later infancy.

In only one case, No. 2, of my own series, was jaundice mentioned as an associated symptom. In this case the connection was not quite clear. The jaundice was so intense as to suggest malformation of the bile ducts, yet no obstruction was found at autopsy either in the cystic or hepatic ducts. It was apparently due solely to catarrhal swelling of the mucous membrane of the ducts.

#### DIAGNOSIS

The gastro-intestinal symptoms preceding duodenal hemorrhage are usually of a mild type and subacute, so that enterocolitis with its frequent bloody and mucous stools is not likely to be confounded with ulcer. There is lacking also the persistent vomiting (not bloody), the paroxysmal pain, the tenesmus, with the passage of blood and mucus from the bowels, but no fecal matter, all of which are characteristic of intussusception; although the age of the patients, the suddenness of the invasion and the acute prostration somewhat suggest it. With blood appearing both in the vomitus and in the stool one might be in doubt as to whether the lesion was gastric or duodenal. The far greater frequency of duodenal ulcers of course makes this lesion much the more probable one.

In the case of symptoms pointing to acute perforative peritonitis in an infant, duodenal ulcer should be remembered as one of the possible causes and next to appendicitis probably the most frequent one.

From what has been said it will be evident that the diagnosis always has been and still is a matter of much difficulty, and it is not surprising

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9. Dusser: Thèse, Paris, 1889.



that the disease has been recognized only at autopsy in the great majority of the cases reported. There is one method of diagnosis which I believe is likely to assist materially in these very obscure cases—the passage of the duodenal catheter. An opportunity to try it was afforded in one of my cases (Case 2). Ulcer was not at first suspected in this patient, but on account of the intense jaundice Hess's duodenal catheter was introduced to see if the presence of bile in the intestine could be demonstrated. On its withdrawal the catheter was found to contain a clot of blood, but no bile. Although the duodenal catheter had been passed many times before in other patients, blood had never been seen under such circumstances. We did not, therefore, believe it could be the result of traumatism. The suspicion of duodenal ulcer was strengthened by the presence of blood in the stools. Given a young infant with intestinal hemorrhage and showing no other symptoms of colitis, intussusception, polypus, etc., the introduction of the duodenal catheter is not only justified, but indicated, and it may give, as in my own case, very definite information on which in the future successful treatment may possibly be based. I know of no other means of diagnosis which will tell as much. The possibility of doing harm by the catheter cannot be denied; but the risk in my opinion is so slight that it may be ignored.

#### PROGNOSIS

In a condition so difficult of diagnosis and where the great majority of the cases are recognized only at autopsy, there are but few data available for prognosis. That such cases may recover seems certain from the observation of Schmidt, who found at autopsy in an infant dying of some acute infection at 5 months the cicatrix of an old ulcer, and also from one of Helmholtz's cases in which recovery followed after an attack with fairly typical symptoms. The probabilities are that such a termination is a very infrequent one. The fatal outcome is due quite as much to the condition of the patients in which most of the ulcers are seen as to the ulcer itself.

#### TREATMENT

Regarding treatment, little can be said; medical treatment is to be symptomatic only, and surgical treatment is as yet inadvisable in most cases.

#### REPORT OF PERSONAL CASES

##### CASE 1.—*Perforating duodenal ulcer followed by general peritonitis.*

*History.*—D. M., a female child, 3 months old, admitted to Babies' Hospital because of loss of weight, vomiting and constipation. Family history unimportant; ninth child; plump at birth; no breast feeding, and had never thriven. The previous history suggested pyloric stenosis; there had been frequent vomiting since the child was 2 weeks old. This occurred after nearly every feeding and was forcible, but the food had been principally milk formulas rather high



in fat. Examination showed a poorly nourished infant of the marasmic type; weight but 5 pounds, 7 ounces. Except for the presence of a moderate degree of thrush and erythema of the buttocks, the physical examination was negative. The abdomen was normal; there were no peristaltic waves and no pyloric tumor; heart and lungs normal.

The infant was placed on a skimmed milk formula containing fat 0.60; sugar 6.00; protein, 1.20 per cent. The child lived eight days after admission, during which time she vomited in all but six times, twice on the first day, twice on the second day and only twice thereafter. The vomiting was not forcible. The appetite was good; the child generally took her food well. The bowels moved usually twice a day; for the first three days the stools were yellow, smooth and well digested; afterwards they were yellow and thin, but never frequent, and no blood was present. Even from the beginning the prostration was marked. The temperature was habitually subnormal in spite of artificial heat and the use of a cotton jacket. The loss in weight continued for the first four days, after which the child became somewhat edematous. During the last three days in the hospital the temperature was not above 95 F. Death occurred quite unexpectedly in a condition of collapse. There was no marked abdominal distention and no tenderness was noted.

*Necropsy.*—Permission to examine the brain was not obtained. The heart and lungs showed nothing of importance. On opening the abdominal cavity the parietal peritoneum and omentum were found much congested and showed numerous small hemorrhages. The peritoneal cavity contained about 70 c.c. of turbid yellow fluid, which after standing deposited a heavy precipitate of pus cells. The cause of the peritonitis was found to be a perforating duodenal ulcer. It was situated on the posterior wall just below the pylorus. It was circular, about 5 mm. in diameter and had a typical "punched out" appearance. No signs of repair at its borders. The mucous membrane of the intestine was blood-stained, but no other lesions were present. The stomach was congested but showed no ulcers. Cultures from the peritoneal fluid showed the streptococcus and colon bacillus. Streptococci were also obtained from the heart's blood and lungs.

Microscopical examination of the ulcer was made by Dr. Martha Wollstein, pathologist to the hospital. There was no inflammatory reaction, but a loss of substance which at one point involved all the coats of the intestine. The edges of the gap were sloping, not undermined. The walls of the mucosa, submucosa and muscular coats forming the edge of the ulcer had undergone necrosis and were converted into a granular, poorly staining layer. The epithelial layer of the mucosa was degenerated or absent for some distance beyond the borders of the ulcer; beyond this the duodenal wall was normal. The adherent pancreas was also normal.

*CASE 2.—Two ulcers in the duodenum; intense jaundice; intestinal hemorrhage; death from marasmus.*

*History.*—M. N., a male Italian child, 2 months old, was admitted to the hospital on account of marked jaundice and progressive loss of weight. The parents were not very intelligent and no detailed previous history could be obtained. It was ascertained, however, that the child was born at full term after a normal labor and had been breast fed up to admission. It had never thrived. Jaundice was first observed two weeks before and had steadily increased. The stools were gray and the urine stained the napkins. The history of the jaundice, given by the parents, was corroborated by a physician who had previously seen the patient.

Examination on admission showed a small, wretched looking infant; weight 5½ pounds. The jaundice was intense, the skin being of an olive-green hue. The sclerae and mucous membranes were also stained with bile. Nothing of importance was discovered in the head, neck or chest. The abdomen was

tyimpanitic, only moderately distended, the circumference being  $13\frac{1}{2}$  inches. The lower border of the liver was felt just below the costal margin; the spleen was not palpable. No abnormal masses were felt.

The child was placed on a milk formula having the following percentages: Fat, 0.60; sugar, 5.00; protein, 1.20 per cent. This patient also lived eight days after entrance into the hospital. During this time the temperature was much of the time subnormal, 94 F. being noted on one occasion. The urine gave a strong reaction to bile, but contained no blood or casts; urobilinogen test negative. All the stools were white, pasty, offensive and large for the food taken. The presence of bile salts could not be demonstrated. The stools contained immense quantities of fat which formed approximately 90 per cent. of the dried residue. This was chiefly in the form of soaps, although there was also a large excess of neutral fat. There was both macroscopic and occult blood in the stools. At no time was there diarrhea, and there was no vomiting of blood. Both Wassermann and tuberculin tests were negative. Blood examination at the time of admission showed: Hemoglobin, 55 per cent.; red cells, 3,900,000; white blood-cells, 15,000; polymorphonuclears, 23.3 per cent.; lymphocytes, 76.3 per cent.; eosinophils, 0.3 per cent. One week later the hemoglobin was but 20 per cent. and red cells, 1,700,000.

The duodenal catheter was passed without much difficulty to ascertain the presence of bile. None could be obtained but on withdrawing the tube it was found to contain a blood-clot. This was repeated three or four days later and a larger clot obtained. The child grew progressively worse and died of exhaustion. From the presence of blood in the stools and in the duodenal catheter the diagnosis of duodenal ulcer was made.

*Necropsy.*—Body emaciated and deeply jaundiced, and all the internal organs deeply bile stained; a small area of bronchopneumonia in right upper lobe; heart normal; pancreas and peritoneum normal; spleen, normal in size and appearance. Liver, dark greenish color, not enlarged and not hard; capsule thickened, especially at the border; slight increase in the connective tissue; no recent exudate; gall-bladder contained thick, dark green bile which could easily be expressed through the duct into the duodenum. Cystic and hepatic ducts appeared normal. Duodenum showed two small round "punched-out" ulcers, each about 5 mm. in diameter. One was situated just below the pylorus (Fig. 1). It extended quite to the peritoneal coat; at its margin was seen a small blood-clot from a bleeding vessel; a large blood-clot in the duodenum lower down. The other was similar in appearance and situated 1 cm. lower down in the duodenum. The rest of the intestine, both small and large, showed areas of congestion and enlargement of the solitary follicles. The kidneys were normal, except jaundiced. Cultures from the lung showed Gram-negative bacilli and pneumococci.

Microscopical examination by Dr. Wollstein showed a loss of epithelium of the mucosa, edema of the mucosa and submucosa, but no cellular infiltration. The muscular and peritoneal coats were normal. The liver showed no increase of connective tissue. The blood vessels and capillary bile ducts were normal.

*CASE 3.—Single ulcer of the duodenum; concealed hemorrhage; sudden death.*

*History.*—M. F., a female child, 4 months old, admitted to hospital on account of diarrhea and vomiting which had lasted one week. Family history unimportant. For the first two months the baby had been breast fed and did well; then had been put out to board and had not thriven. The bowels had been generally loose, but no vomiting had been noted till one week before admission. Stools thin and green, four or five daily; no fever, but steady loss in weight.

On admission the child weighed 8 pounds, 14 ounces; fairly well developed; did not appear acutely ill; heart and lungs normal; spleen palpable one-half inch below costal margin; liver, enlarged, the lower border  $1\frac{1}{2}$  inches below the costal margin; Wassermann negative. Blood: hemoglobin, 60 per cent; red cells, 4,400,000; white cells, 14,000; polymorphonuclears, 40 per cent.; lymphocytes, 60 per cent.

The child was put on protein milk (*Eleccismilch*) 4 ounces every three hours. No further vomiting occurred after admission. The stools continued from four to six a day and for the most part were thin and of a grass green color; no macroscopic blood. The temperature remained normal for four days when it rose to 101.4 F., later to 102.6 F. Until this day the child did not appear seriously ill and looked much the same as during the previous four days. A marked pallor was then noted, the patient looking almost exsanguinated, though no blood was seen in the stools and no other hemorrhage had been observed. Death occurred quite suddenly on this day, almost without warning.

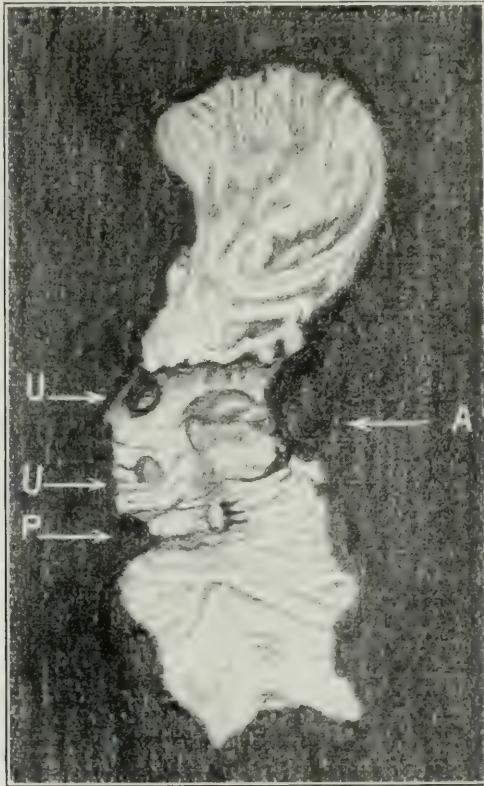


Fig. 1.—Two ulcers in the duodenum. Case 2. A, artefact; U, ulcers; P, papilla.

*Necropsy.*—Body well nourished; small areas of atelectasis in lungs but no pneumonia; liver extremely fatty, with a few small subcapsular hemorrhages especially on the under surface. The stomach contained a large amount of blood-stained fluid and showed many submucous hemorrhages, but no ulcers. The stomach contained one large soft, dark red clot which extended into the duodenum. Three millimeters below the pyloric valve on posterior wall (Fig. 2), there was an oval ulcer, 4 by 8 mm., edges sharply defined; no surrounding inflammation. At the base of the ulcer small clots and a bleeding point were discovered. The ulcer had the typical “punched-out” appearance; it extended through the muscular coat to the peritoneum. Mucous membrane in the neigh-



borhood was pale. The rest of the small intestine showed nothing abnormal. Nothing of importance in the other viscera.

Microscopical Examination by Dr. Wollstein: The normal mucosa showed an abrupt solution of continuity without any inflammatory products. The epithelial layer and Brunner's glands had disappeared leaving an irregular, narrow, glandular, poorly staining layer internal to the muscularis mucosa. The submucosa contained no Brunner's glands, but showed no inflammatory products. The muscular coats were normal. The duodenum on either side of the ulcer was quite normal, even the epithelial covering being intact.

CASE 4.—A single ulcer of the duodenum, with multiple erosions in the mucous membrane of the stomach in a newly born child; no hemorrhages present.

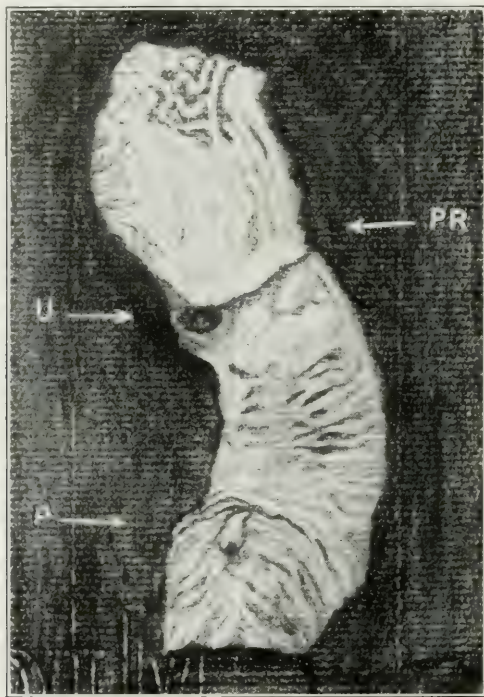


Fig. 2.—A single ulcer of the duodenum in the usual situation. Case 3. U, ulcer; P, pabilla; P. R., pyloric ring.

*History.*—R. D., a male child, 12 days old, was admitted for vomiting and diarrhea which had existed almost from birth. The infant was one of twelve, five of whom were living and six dead; all from marasmus, the history stated. The birth was at term and the labor normal. No breast feeding had been given; at first the food had been condensed milk, afterwards nothing but barley water. All the food had been poorly taken and much of it had to be forced. The stools had never been normal; for a few days before admission they had been from two to five daily, thin, of a yellow-green color and contained mucus. Vomiting had occurred after almost every feeding. The stomach was emptied two and a half hours after feeding and was found to contain a small amount of mucus, but no blood.

On admission the child was in extremely bad condition, very feeble, almost moribund in fact; weight six pounds. No local evidences of disease in the



abdomen; râles at the bases of both lungs; no nervous symptoms; temperature normal.

The child was put on a weak milk formula, fat 0.90; sugar, 5.00; protein, 0.70 per cent., and castor oil was administered. On the following day the temperature rose to 104.6 F. and remained above 102 F. the entire day. Vomiting continued, though but little food was taken. The stools never contained blood but were frequent, thin and green, at times only a stain on the napkin. There was no improvement in any of the symptoms and death occurred forty-eight hours after admission.

*Necropsy.*—Body wasted; nothing of importance in thoracic organs; liver, fatty and slightly congested, no increase in connective tissue; pancreas congested; kidneys showed uric acid infarcts in many pyramids.

The stomach contained blood-stained mucus and the mucous membrane showed many erosions extending quite to the muscular coat. They were of irregular shape, some rounded and some elongated. They were below the rugae rather than on them. In the duodenum was an ulcer 4 by 8 mm. situated on the anterior wall, about 1 cm. below the pylorus and 1 cm. above the papilla. It had a bile stained base; edges congested and elevated. Elsewhere the duodenum appeared normal. The rest of the small intestine showed intense congestion, but no hemorrhages and no ulceration. The solitary follicles of the colon were generally swollen. There was swelling and congestion of the mesenteric lymph-nodes.

I wish to acknowledge my indebtedness to Dr. Stafford McLean for assistance in collecting the literature and to Dr. E. A. Morgan for the drawings of the pathological specimens.

#### SUMMARY OF LITERATURE ON DUODENAL ULCERS IN INFANCY

The earliest cases reported in the new-born were collected by Dusser<sup>9</sup> in 1889. In thirty-one collected autopsies on gastro-intestinal hemorrhage in the new-born there were five in which duodenal ulcer was found. These are as follows:

Spiegelberg:<sup>10</sup> Case 1. On the fourth day, suddenly, hemorrhage from the stomach and intestine; death in a few hours. Stomach showed ecchymoses only. The duodenum showed round ulcer close under the pyloric valve; swelling in the follicles of the large intestine; no other lesion. Case 2. Thirty hours after birth sudden occurrence of bloody vomiting and shortly afterwards bloody stools; death in twenty-four hours. The stomach contained 30 c.c. of fresh blood; the mucous membrane was normal. Midway between pylorus and papilla a large coagulum in the duodenum; in the posterior wall one large and two smaller ulcers.

Landau:<sup>11</sup> An infant dying on the fifth day had bloody vomiting and bloody stools. Necropsy: Large clots in the stomach; mucous membrane normal. Round ulcer in the duodenum 5 cm. from the pylorus, size 5 by 8 mm. Rest of the intestine and mucous membrane normal.

Kling:<sup>12</sup> Death on the fourth day. Symptoms, vomiting of blood and bloody stools. In second portion of duodenum, posterior wall, ulcer, 1 by 1.5 cm., perforated at one point.

Zeischwitz:<sup>13</sup> Thirty hours after birth copious hemorrhage from the rectum; arterial blood. Death the following morning. In the posterior wall of the duodenum a little above the papilla an ulcer going to the muscular coat; an artery opened; intestines elsewhere normal.

More recently Gruber in a report of seventeen cases under 10 years old, mentioned two duodenal ulcers in the new-born.

10. Spiegelberg: *Jahrb. f. Kinderh.*, 1869, p. 333.

11. Landau: *Ueber Melena Neugeborenen*, Monograph, Breslau, 1874.

12. Kling: *Ueber Melena Neonatorum*, Inaugural Dissertation, München, 1875.

13. Zeischwitz: *Schmidt*, 1888, xxxv.

Schmidt<sup>2</sup> reports one case in an infant five days old, and one of my own cases, an infant 12 days old, should probably be included in this group.

The principal reports of cases of duodenal ulcers in later infancy are the following:

Veit:<sup>14</sup> An infant 1 week old, previously healthy; sudden onset, pain, fever, anorexia; death in thirty-six hours; no blood in stools or vomitus. Necropsy: coffee-ground material in stomach and intestines; large blood-clot in the duodenum; two duodenal ulcers on posterior wall; no perforation.

Adriance:<sup>15</sup> An infant 10 months old suffering from marasmus with marked gastro-intestinal symptoms for two weeks. Vomiting persistent, but vomitus contained no blood. Four days before death blood from the rectum following intestinal irrigation. After this two or three bloody stools daily until death. Necropsy: bright and dark blood in stomach; a duodenal ulcer, 1 by 2 cm., just below pylorus on posterior wall, going through all the intestinal coats.

Borland:<sup>16</sup> An infant 8 months old; severe general pustular eczema; gastro-intestinal symptoms for three days; vomiting of blood; no mention of blood in stools. Necropsy: round ulcer just below pylorus on posterior wall; large mass of clotted blood in peritoneum; no peritonitis.

Torday:<sup>5</sup> An infant 8 months old, admitted for atrophy and rickets; shortly after began to vomit in a manner characteristic of pyloric stenosis. This continued in spite of diet changes, stomach washing, etc. No blood in the vomitus or stools. Peristaltic waves present. Pylorus, not palpable. Death six weeks later. Necropsy: stomach greatly dilated; no pyloric stenosis; but ulcer 5 mm. below pylorus; blood in the intestines. Author believes that pyloric spasm was caused by the ulcer.

Entz,<sup>1</sup> quoted by Flesch: In 364 autopsies on infants under 1 year, ten duodenal ulcers and one gastric ulcer; ages between 6 weeks and 5 months. Two perforated and caused a purulent peritonitis. Death in three from hemorrhage. In most cases definite gastro-intestinal symptoms with infantile atrophy preceded. Diagnosis usually made at autopsy only.

Küttner:<sup>17</sup> Patient 1 month old; seven days after birth vomiting, diarrhea and for two days bloody stools. Twenty-three days later vomiting of blood and death. Necropsy: A single round ulcer upper part of duodenum, 5 mm. in diameter. Author reports also a case in a child 4 years old. Refers to Collin's monograph<sup>18</sup> who in 279 cases of duodenal ulcer found seventeen under one year.

Finny:<sup>6</sup> An infant, 2½ months old, had been vomiting almost from birth in spite of stomach washing, etc. Pyloric stenosis diagnosed; later bloody stools led to a suspicion of duodenal ulcer, confirmed by autopsy. Two ulcers present 1.5 cm. below pylorus in posterior wall; one had perforated; pylorus contracted and its muscular coat thickened.

Sochaczewski:<sup>19</sup> An infant 5 months old; gastro-intestinal symptoms since 4 weeks old; general condition wretched. During the last twenty-four hours three to four large bloody stools; no vomiting. Necropsy: single ulcer in posterior wall two fingers' breadth below pylorus. Peyer's patches swollen but no other ulcerations.

Helmholz<sup>3</sup> (first communication 1909): Reports nine cases of duodenal ulcer of which eight came to autopsy. Five of these were between three and five weeks old; three between 2½ and 4 months. All were in atrophic children. A single ulcer was present in four of the eight cases. Intestinal hemorrhage was noted in four; in four others no definite local symptoms. In the child who recovered

14. Veit: *Deutsch. med. Wchnschr.*, 1881, p. 681.

15. Adriance: *Arch. Pediat.*, 1901, p. 277.

16. Borland: *Lancet*, London, 1903, ii, 1084.

17. Küttner: *Berlin Klin. Wchnschr.*, 1908, xlv, 2009.

18. Collin: *Thèse*, Paris, 1890.

19. Sochaczewski: *Arch. der Kinderkr.*, 1909, l. 25.

the diagnosis rested on the sudden development of marked prostration; almost collapse, followed by intestinal hemorrhage which lasted three days. Patient was an infant 2 months old and was well five months later. In a second communication (1909), he reports seven additional cases; like the former ones these were seen in different German clinics; all of these patients were likewise atrophic infants. In three intestinal hemorrhage occurred and in one of these there was also perforation; in four there were no definite symptoms. Six of these patients were between 1 and 3 months old and one was 7 months. In three of the cases a single ulcer was present; in four two or more.

Griffith:<sup>20</sup> An infant 6 months old; symptoms for two days; vomiting followed shortly after by trace of blood in the stools. On the following day vomited clear blood several times and one large hemorrhage from the bowel; death in collapse. Necropsy: ulcer, 5 mm. in diameter, in posterior wall of duodenum just below the pylorus. Ulcer extended through the intestine, but adhesions prevented the escape of fluid into peritoneum. Stomach contained 1 ounce of bloody fluid.

Hertz:<sup>21</sup> An infant 2½ months old, artificially fed. Frequent bloody stools for two days, followed by death. A single ulcer in the upper part of the duodenum, 1.5 by .75 cm. in diameter.

Gruber:<sup>22</sup> In 4,208 autopsies, 1,147 peptic erosions, scars or ulcers; 17 duodenal ulcers in children under 10 years; six in infants between 3 and 8 weeks; details not given.

Weill<sup>23</sup> and Gardère: An infant 1 month old; digestive disturbances from birth with diarrhea and irregular vomiting; traces of blood noted in stools, but no real bleeding. Case regarded as a delayed hemorrhage in the new-born, due to intestinal lesion. Necropsy: a single ulcer just below pylorus; blood-clot in the duodenum.

Flesch:<sup>24</sup> An infant, 3 months old, atrophic, anemic, losing weight. Symptoms for last fifteen hours; large, bloody stools; subnormal temperature; death in collapse. Necropsy: two ulcers, one just below pylorus and one just above papilla; follicular gastro-enteritis present.

Schmidt:<sup>2</sup> In 1,109 necropsies on infants in the first year, twenty cases of duodenal ulcer. Most of the patients in poor general condition; ten were atrophic. They were seen associated with a great variety of conditions — rickets, whooping-cough, nephritis, empyema, meningitis, pyloric stenosis. Author thinks no closer association with atrophy than with any other condition of marasmus. Of the twenty cases, peritonitis was present in three and hemorrhage in seven. In ten, ulcers were latent. The usual situation was just below the pyloric ring.

Birk<sup>8</sup> (quoted by Helmholz, unpublished): Eight cases; ages eight weeks to ten months. Three with pyloric stenosis; one with pylorospasm; two in normal infants who were well up to a day or two before death from hemorrhage; two with acute pneumococcus infections.

14 West Fifty-Fifth Street.

20. Griffith: New York Med. Jour., Sept. 16, 1911.

21. Hertz: Referat im Hospitalstidende, 1911, liv, 35.

22. Gruber: Referat im München. med. Wehnschr., 1911, lviii, 1668.

23. Weill and Gardère: Lyon méd., 1911, cxvii, 1177.

24. Flesch: Jahrb. f. Kinderh., 1912, lxxvi, 542.

25. Fischl: Pfaunder and Schlossmann, Am. Ed., 1908. iii, 149.



## CASEIN IN INFANT FEEDING. EXPERIMENTS IN EXACT PERCENTAGES \*

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The proteins of cow's milk have been the source of much interesting discussion and controversy among pediatricians. Theories as to their digestibility are changing almost yearly. Whey proteins advocated by Rotch have given place to the "whole proteins" of Czerny, Keller and Walls (which bring forward the digestibility of skim-milk); while others have heated, peptonized and lately precipitated the proteins in further attempts to improve our knowledge and treatment. Up to the present the proteins of milk formulas have not received the attention we should expect. Protein requirements have painstakingly been estimated and the formulas prescribed, but no one has seriously questioned the accuracy of such mixtures. Several days during the summer of 1912, formulas made according to Finklestein's method were found on examination to contain proteins varying from 2.5 to 4.5 per cent. This instance of error led us to investigate the composition of home modifications and laboratory milk formulas.

### METHODS OF ANALYSIS

1. *Total Protein*.—Total nitrogen was determined by Folin's modification of Kjeldahl's method. Total nitrogen multiplied by 6.37 gave the total protein.

2. *Casein*.—Casein was determined by the volumetric method devised by Van Slyke and Bosworth<sup>1</sup> of the New York Agricultural Experiment Station.

"Its operation in the determination of casein in a sample of milk requires only from twelve to fifteen minutes and the result was reasonably accurate, usually coming within 0.1 to 0.2 per cent. of the correct amount." This method requires the simplest and most inexpensive equipment. It further is eminently practical in the hands of unskilled persons after a minimum of instruction.

3. *Albumin*.—Albumin when determined was found by subtracting the per cent. of casein from the per cent. of total proteins.

### STUDY OF PERCENTAGES OF CASEIN IN LABORATORY MILK FORMULAS

In Table 1 will be found the results obtained from the examination of twenty mixtures obtained from a food laboratory. These were made from 32 per cent. cream, fat-free milk, whey, etc., from a reliable source. In each case the prescribed formulas are given, while in the last column the

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\* From the Massachusetts Babies Hospital, 106 Chestnut Avenue, Jamaica Plain, Mass.

\* Read at the meeting of the American Pediatric Society, Washington, D. C., June, 1913.

1. Van Slyke and Bosworth: New York Med. Jour., Sept. 18, 1909.



amounts of variations from these formulas are seen. It will be noticed that in every case the total protein found was less than that called for. No determinations of fats or sugars were made. If as much error occurred with them as was found with the protein, many of the formulas would have been very deficient in caloric value. These errors we at first

TABLE 1.—PERCENTAGES OF CASEIN, ETC., IN LABORATORY MILK FORMULAS

Sample	Formulae Prescribed			Found		Error
	Fat	Sugar	Protein	Casein	Protein Total	
1	4.0	7.0	1.50	1.1	1.2	(—) 0.3
2	4.0	6.0	1.60	1.3	1.4	(—) 0.2
3	4.0	7.0	2.50	1.5	2.1	(—) 0.4
4	4.0	7.0	2.00	1.4	1.8	(—) 0.2
5	2.5	7.0	.50-1.20	1.4	1.4	(—) 0.3
6	2.25	5.0	.90-0.25	0.3	0.9	(—) 0.2
7	1.70	7.0	0.89	0.7	0.7	(—) 0.1
8	2.75	6.0	1.25	0.9	0.8	(—) 0.4
9	4.0	7.0	1.50	1.0	1.0	(—) 0.5
10	3.9	6.5	2.10	1.3	1.6	(—) 0.5
11	4.0	7.0	2.00	1.4	1.6	(—) 0.4
12	3.75	6.75	1.50	1.2	1.2	(—) 0.3
13	3.60	6.50	.90-0.50	0.7	1.0	(—) 0.4
14	4.0	7.0	2.25	1.4	1.9	(—) 0.3
15	4.0	7.0	2.50	1.5	2.2	(—) 0.3
16	3.75	6.75	.90-1.00	1.2	1.7	(—) 0.2
17	4.0	6.75	1.50	1.1	1.3	(—) 0.2
18	3.25	5.50	3.25	1.7	2.7	(—) 0.3
19	4.0	7.0	1.75	1.4	1.6	(—) 0.1
20	2.50	5.50	0.75	0.6	0.6	(—) 0.1

TABLE 2.—ANALYSIS OF PERCENTAGE CREAM AND MILK

Date	32% Cream			16% Cream			4% Milk			F. F. Milk			Whey		
	T. P.	Cas.	Alb.	T. P.	Cas.	Alb.	T. P.	Cas.	Alb.	T. P.	Cas.	Alb.	T. P.	Cas.	Alb.
April 21	2.28	1.5	(0.78)	2.50	1.6	(0.90)	2.76	2.0	(0.76)	3.16	2.2	(0.96)	0.78	0.0	(.78)
April 22	2.10	1.4	(0.70)	2.58	1.5	(1.0)	2.88	2.1	(0.78)	3.08	2.1	(0.98)	0.87	0.0	(.87)
April 23	2.17	1.5	(0.67)	2.70	1.7	(1.0)	2.97	2.1	(0.87)	3.19	2.2	(0.99)	0.87	0.0	(.87)

put down to irregularities in the milk and cream used in making the mixtures. On examination of these products, however, we found that they were fairly uniform in composition, as is shown by the figures in Table 2. The greatest variations are found with the creams, but the actual error caused by these variations would be very small, as the creams are always diluted with the other ingredients in the mixture.

## STUDY OF PERCENTAGES OF CASEIN IN HOME MODIFIED FORMULAS

Table 3, in contrast with Table 1, gives the results of examination of fifteen home modifications. These were made from 10 per cent. cream and fat-free milk which were furnished by a reliable dairyman. It will be noticed that only six of the fifteen mixtures contained less protein than the formulas called for, while the average error is much less than in the case of the mixture prepared in the food laboratory. We can give only one feasible explanation for the variations and deficient proteins found among the laboratory formulas, i. e., that there is a lack of careful technic on the part of those concerned in making the mixtures correspond more closely to the prescribed formulas.

TABLE 3.—ANALYSIS OF HOME MODIFICATIONS

Sample	Formulae Prescribed			Found		Error
	Fat	Sugar	Protein	Casein	Total Protein	
1	2.0	6.0	1.00	0.85	1.05	( ) 0.0
2	2.0	4.0	1.50	1.4	1.85	(+) 0.3
3	2.5	6.5	2.75	2.0	2.8	(+) 0.1
4	1.25	6.5	1.25	1.0	1.37	(+) 0.1
5	2.0	6.5	1.2	0.85	1.16	(-) 0.1
6	1.75	7.0	1.5	1.2	1.5	(-) 0.0
7	2.0	6.5	1.5	1.3	1.7	(+) 0.2
8	3.25	7.0	1.75	1.1	1.6	(-) 0.1
9	2.0	6.5	1.6	1.0	1.4	(-) 0.2
10	1.25	6.5	1.2	0.8	1.1	(-) 0.1
11	2.0	6.5	1.6	1.4	1.8	(+) 0.2
12	2.25	6.5	1.6	1.0	1.4	(-) 0.2
13	3.25	7.0	1.7	1.2	1.6	(-) 0.1
14	2.0	7.0	1.5	1.1	1.5	( ) 0.0
15	2.0	3.0	2.0	1.7	2.2	(+) 0.2

## POSSIBLE METHODS OF OVERCOMING THIS DEFICIENCY OF PROTEIN

There are three methods of making up formulas which will give a more exact casein content: (a) Secure cream and skimmed-milk from a reliable dealer and have him furnish proper analysis of the same. From the analysis a mixture of any desired composition can be made with a few simple calculations. This method is recommended for home use under the direction of a physician. (b) Recommended for hospitals and institutions: Secure cream and fat-free milk. Determine the percentage of fat in the cream by the Babcock test. Determine the percentages of casein in the cream and fat-free milk by the volumetric method of Van Slyke and Bosworth.

The percentage of casein multiplied by 1.4 would give the percentage of total protein (or a figure which is close enough to it for all practical

purposes). By the use of simple calculations, mixtures can be made which will vary from the formula by about 0.1 of protein. (c) This method is in the experimental stage and is not recommended for general use at present. The desired mixture is made by using the necessary amount of cream, whey, etc., and dry powdered casein or paracasein. The percentages of fat and protein in the cream are determined and the whey is assumed to contain 0.9 per cent. protein. (N. B. It is quite important that some whey be used, as it furnishes the inorganic constituents demanded by the growing baby. The proper amount of whey to be used has not been accurately worked out as yet.) The amount of protein necessary to complete the formula is secured by adding in the form of dry powder, casein or paracasein.<sup>2</sup>

## EXPERIMENTS WITH DRIED POWDERED PARACASEIN

One of the preliminary experiments which was carried out is seen in the following. It was undertaken to determine the digestibility of formulas made with dry powdered casein.

TABLE 4.—ANALYSIS OF FORMULAS IN AUTHOR'S EXPERIMENTS

Experiment	Date	Formula			Protein in Food by Analysis	Volume Taken	Nitrogen			
		Fat	Sugar	Prot.			Ingested gm.	Excreted gm.	Retained gm.	
	April							Urine	Feces	
1	{ 12	2	4	2	1.93	1134	{ 6.9	4.90	.54	1.46
	{ 13	2	4	2	1.93	1134				
2	{ 16	2	4	2	1.90	1134	{ 6.8	4.21	.39	2.20
	{ 17	2	4	2	1.90	1134				

The patient, H. A., was admitted to the hospital Jan. 15, 1913, for observation and feeding. The child was apparently normal, fair physical condition, development and digestion. April 12 the experiment was started. Up to this time the child had been gaining well. His movements were one to two a day, normal, giving no signs of fat, carbohydrate or protein indigestion. His temperature was normal and disposition happy. On April 12 he was placed on the metabolism bed. The food given from April 12 to 16 was made from ten per cent. cream, fat-free milk, lactose and water and had the composition indicated in Table 4 (Experiment 1). Urine and feces were collected for a forty-eight hour period, the feces being marked off by carmin red. The figures obtained are also given as Experiment 1, Table 4. The child took the food well, had no temperature, gained in body weight and remained normal in every respect. On April 16 the food was changed. The percentage composition remained the same, but the materials used were different; cream, whey, lactose, lime-water and dry powdered paracasein. The food was well taken, the child's well being and general

2. Bowditch: Boston Med. and Surg. Jour., May 15, 1913, p. 722.

condition continued normal. no rise in temperature developed, he gained in weight and his movements were perfectly smooth and digested, but more formed. The urine and feces were collected for a period of forty-eight hours as before and the figures obtained are given as Experiment 2, Table 4.

From the foregoing we can safely say that laboratory formulas are frequently deficient in protein; that home modified mixtures compare far more favorably on this point. That it does not seem to be the fault of the constituents which go to make these mixtures, but rather the care of those who put up such formulas.

We feel that we have proved that formulas with exact percentages of protein can be obtained by determining the percentage of casein in the creams and milks used, and further, that powdered dry casein and paracasein can be used in making up shortage of protein in place of fat-free or skim-milk. We will also show in a later publication that this powdered dry casein or paracasein is very easily digested, and is capable of furnishing all the protein requirements of the growing baby.

This procedure of accurate determination of protein may or may not be of service. It remains to be seen how far it can be used. It is certainly not necessary to go into such details in general, but special cases may bear more fruit when we consider the possible errors and the resultant under-feeding of protein as we have illustrated above. This is the beginning of a series of experiments to be continued along similar lines.

We wish to express our thanks to Dr. Helen Dudley of Brooklyn, New York, for her interest and time.



## PAROTITIS COMPLICATED WITH MENINGITIS \*

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The appearance of nervous troubles in the course of parotitis did not escape the attention of the older observers. Hamilton in 1758 recorded a case of death in a man of 22 years from meningitis complicating mumps; Astley Cooper the case of an infant who died after an illness of eight days; French in 1812, Malsbrouche in 1867 and Niemeyer have described these conditions without detail. Trousseau relates cases of men 17 and 35 years of age with severe meningitis which disappeared when orchitis supervened.

Gailhard in 1877 compared the meningitis and cerebral complications of mumps to rheumatism of the brain. He reported six cases with stupor, feebleness, slowness of pulse, rigidity of neck, headaches, hyperesthesia, photophobia, delirium and coma. In 1885 Lannois and Lemoine published an important memoir on this subject. They reported a case in which the meningeal complication of mumps was followed by aphasia and right hemiplegia, and was not well for some months. They considered these conditions to be dependent on meningeal lesions of the congestive and inflammatory order accompanied sometimes by lesions of the brain.

Dupre in 1884 proposed the term meningism for these cases, holding there was not a true anatomical alteration of the brain. In some epidemics parotitis appears to lose its benign qualities and causes grave symptoms. Writers have observed meningitis often in cases which have orchitis and are led to believe that such cases are more severe, yet in children, in whom orchitis rarely occurs, meningitis has been noted in a number of cases. The infant has a nervous system easily impressed, which has a tendency to respond to irritating morbid agents by an intense reaction, such as convulsions. This is increased by heredity, neuropathy and alcoholism. Acute meningitis is usually described under three periods: invasion, excitement and depression; each of these periods is marked by a series of symptoms which taken together make a clinical picture, as a rule, constant and characteristic. Such a description cannot be made in the meningitis of mumps. It is true that it may present all the symptoms of acute meningitis, but usually the symptoms take a variable course; nervous complications are tolerably frequent, due to the

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\* Read at the meeting of the American Pediatric Society, Washington, D. C., May, 1913.

involvement of both the central and the peripheral nerves. A meningeal reaction may present itself in connection with an attack of mumps, coming on two or three days after the swelling of the parotids, although in some cases it supervenes rather later. On the other hand, it has been known to precede the parotid enlargement by some hours.

#### SYMPTOMS

The meningitis in question manifests itself by a rise in temperature, headache, insomnia and general discomfort. As a rule, the pulse does not increase in rapidity in proportion to the rise in temperature. In exceptional cases the symptoms are much more severe, there is a sharp rise of temperature, with nausea, vomiting and constipation, there is some rigidity of the neck, Kernig's sign, pupillary changes, strabismus, showing an irregularity of the pulse, disturbance of sensation, and even paralysis of the cranial nerves. These are obviously symptoms of basic meningitis, which is the usual form in this connection. In some instances there are signs of cerebral irritation, delirium, convulsions, spasmodic contraction of the facial muscles, the tongue and limbs, monoplegia and hemiplegia, deviation of the eyes, aphasia, and among spinal symptoms, cutaneous hyperesthesia and pain in the back and limbs. Lesions of the nerves are sometimes consequent to meningitis or occur independently of it. In these cases the virus of mumps seems to attack the sheaths of the peripheral nerves, as well as the walls of the nerve centers.

Many attempts have been made to explain the nervous complication of mumps. Eichhorst attributed them to hyperemia of the brain due to compression of the internal jugular by the enlarged parotid; Jussoud and Groucher by the embolic bodies from the endocarditis due to the parotitis infection; Micilsky to meningitis; Lannois and Lemoine to a meningo-encephalitis or perhaps a thrombosis of the sylvian artery. Comby attributed them more to an hysteria than parotitis; Gallavardin interpreted them as proving a true meningitis due to the poison of parotitis. According to Schottmüller, a post-parotitic meningitis should be regarded as a serous meningitis, with more or less of an accompanying encephalitis.

For a long time the meningeal symptoms which have appeared in mumps had been described, but their pathological character was disputed, and the terms pseudomeningitis parotitis and meningism parotitis employed to designate them. It was not until lumbar puncture was resorted to that a clear idea was obtained of the nature of these meningeal reactions. This showed that it was not a simple functional trouble, but an anatomical modification of the meninges. When in 1902 A. Monad practiced systematically lumbar puncture in the infants attacked by parotitis, and proved six times in eight a lymphocytosis of the cerebrospinal fluid as abundant as that which exists in tuberculous meningitis,

he demonstrated that this disease is capable of determining an appreciable change in the meninges. The same has been confirmed by Sicard in infants, Chauffard and Boideu in 1904, Dopfer, Netter, Comby, Hutinel, Nobécourt and Brelet and Feliciano in 1907. All found a lymphocytosis in parotitis that had many nervous symptoms. The fluid was clear, with numerous lymphocytes, as in tuberculous meningitis. There was a small amount of albumin, but no fibrin. In the latter disease the meninges are permeable to iodine, but not the first. Dopfer states that in simple mumps the cerebrospinal fluid is normal in cellular elements. The lumbar puncture is useful, not only for diagnosis, but also for treatment, as the severe symptoms yield soon after its employment, as has been demonstrated by Chauffard and Vidal. The lymphocytosis only lasts for a short time.

#### BACTERIOLOGY

That a diplococcus is the pathogenic agent which is the cause of parotitis there can be little doubt from the researches and experiments that have been made. In 1893 Laveran and Catrin described a characteristic diplococcus which they had obtained from the parotid, from the edematous tissue of the face, from joint transudates and from the blood in cases of this disease. In 1896 McCray and Walsh examined the saliva from Steno's duct in ten cases. They found a diplococcus six times. Bein and Michaelis in 1897 and Pick in 1902 reported a similar finding. In 1906 Feissier and Esmein examined the blood in forty-five cases and obtained a diplococcus in thirty-seven. These experiments have been confirmed in this country by Isabella C. Herb of Chicago, who isolated a diplococcus similar to that of the other observers. According to Dopfer, the bacteriological examination of the cerebrospinal fluid and meningeal exudate collected after death was sterile.

In the autopsy made by Maximowitch in 1880 the surface of the brain was found edematous and congested with serofibrinous exudate adherent to the pia-mater; the pons and cord were hyperemic.

In 1,705 cases of parotitis observed, there were 158 cases of meningitis, but this does not give the true proportions, as many cases pass unnoticed by careless observers.

#### DIAGNOSIS

The quick onset would differentiate this from tuberculous meningitis, as the latter comes on slowly and does not tend to disappear; from cerebrospinal meningitis by the clear fluid and absence of the meningococcus. In some cases the parotitis is so slight as not to be noticed, and this adds to the difficulty of the diagnosis.

This meningitis generally disappears rapidly. The motor paralysis can last a long time, but finally gets well. The deafness and optic atro-



phy appear to persist. This usually harmless disease may develop very alarming symptoms and be followed by permanent damage to important organs, and even end fatally. Among the sequelae of the disease Joffroy mentions peripheral neuritis and paralysis of the extremities lasting for months. The meningitis of mumps, while not a common complication, yet occurs often enough to make one employ careful measures during the first two weeks of the disease.

This is an infectious disease, specific and general in its nature, localizing on the salivary glands, but affecting all of the economy. It is the same as the eruptive fevers, of which it partakes in nature, being contagious and epidemic.

#### CASE REPORTS

CASE 1.—R. S., 11 years old, male, colored, was admitted to the Children's Hospital January 7, 1913, with the following history:

*History.*—Mother in good health; father alcoholic; one infant brother in good health. The boy was in perfect health up to his present illness, having had none of the diseases of childhood. About Christmas, 1912, the mother noticed that the child's face was swollen, which condition a physician pronounced mumps, of which there was an epidemic. There was fever, no sore throat, appetite good and bowels open. He had frequent desire to urinate but did so with great difficulty. The urine was of a deep yellow color and moderate in quantity. He could not walk without assistance, and complained of much pain in the legs.

*Examination.*—When he was admitted to the hospital the sides of the face (parotid region) were swollen and there was great swelling and edema of the scrotum (this had come on early in the disease), with marked hypospadias. He took very little notice of surroundings. Lungs, heart and abdominal organs were normal; tongue coated; old ulcer left cornea; child unable to stand; dull and apathetic, but would answer questions in a sluggish manner; pupils unequal in size, the left much larger than the right, but reacted to light; patellar reflexes absent; marked Kernig's sign; no Babinsky.

*Course.*—January 8. Irritable, complains of pains in arms and cannot turn alone.

January 15. Can roll from side to side in bed, but cannot raise head and shoulders from pillow or sit up. Most of the time is spent in a drowsy state when not actually asleep. Has control of bladder and rectum.

The child up to this time had been on the surgical service, but was transferred to the medical service and came under my charge. A Wassermann made by Dr. W. W. Wilkerson gave a single plus. The first molars were normal.

January 30. Able to sit up.

February 3. Discharge from left ear.

February 16. Examined by Dr. Tom A. Williams. Right patellar reflex feebly present if reinforced; left absent; diadokokinesis not impaired; heel and knee tests negative; ankle-jerk present; can walk and run with eyes closed without incoordination; sense of deep muscular pain absent in limbs, face and neck. Lumbar puncture was made by Dr. B. M. Randolph and the fluid was found clear with no lymphocytosis. The eyes were examined by Dr. D. K. Shute and pronounced normal.

February 27. Examined again by Dr. Williams. Patellar reflex present in left, slightly. Deep pain sense has been recovered.

March 16. Pupils equal in size; no discharge from ear; reflexes normal; child has gained weight and appears well.



This case presents the following features common to many of the cases reported: Fever, pains, delirium, marked Kernig sign, patellar reflexes absent, unequal pupils and paralysis. There was a slow pulse on several occasions, but never a decided bradycardia. The swelling of the scrotum has been noted several times in adults.

Dr. Williams has made the following comments on the case: The absence of deep reflexes and the loss of the sense of pressure-pain, along with unequal pupils and a positive Wassermann reaction, caused suspicion of tabes dorsalis. Loss of the deep pain conductivity is very commonly a symptom in tabetic radiculitis, but the absence of lymphocytosis rendered the diagnosis most unlikely, especially when the onset of symptoms was so acute as in this case. We know that tabes is merely a sequel of chronic syphilitic leptomeningitis, which invariably shows a lymphocytosis until arrested (see Williams: *Am. Jour. Med. Sc.*, August, 1908). But the case is of great interest as a problem of differential diagnosis, which, in the absence of a cytological examination of the cerebrospinal fluid and the history of mumps, could not have been decided for a long time.

CASE 2.—Boy, 3 years of age, entered the service of Dr. Joseph S. Wall at the Children's Hospital April 23, 1913 with the following history:

*History.*—Father 45 years of age in good health; mother died of tuberculosis nine months previously, 35 years old; otherwise family history good. Birth natural; breast fed for one month only, on account of mother's health. Had always been healthy. Is a well-formed, strong-looking child.

April 14. Complained of pains in the abdomen and had straining of eyes.

April 15. Left side of the neck swollen and the following day the right side became enlarged. Appeared well until April 20, when he became drowsy.

April 22. About 6 p. m. the eyes became set, followed by a convulsion, clonic and then tonic in character, lasting about thirty minutes. Did not regain consciousness until 6 a. m. the next morning.

April 23. Admitted to hospital. Does not recognize anything; cries out as if in pain; vomited milk.

April 24. Right sided convulsions at first, then becoming general, with deviation of the eyes toward the left. Pupils dilated; did not react to light; urine normal; leukocyte count 12,300.

April 25. Very restless, but takes nourishment well. Examination of the cerebrospinal fluid was made by Dr. B. M. Randolph. The fluid came out under great pressure, clear; white cells 90 per cent.; cells mostly lymphocytes; no bacteria found. Leukocyte count of blood 16,500.

April 26. Muscular twitching of face. Pulse was 60 per minute several times during the day.

April 27. Examined by Dr. Tom A. Williams. Reflexes: Patellar, left present; right exaggerated. Ankle clonus present. Babinsky, right equivocal; left, flexion. Abdominal, left faint; right present. Elbow, left faint; right exaggerated. Deep pain sense present. Motility active. Marked strabismus. Not able to analyze. Pupils dilated; right greater than left; no reaction; tache cerebrale marked.

April 28. Seemed in stupor the entire night; pulse slow and irregular at times; convulsions during the afternoon involving the entire body.

April 29. Still in stupor. Restless at times; answered "no" to questions. Lumbar puncture made by Dr. Randolph presented the same characters as the last one.

April 30. Eyes examined by Dr. D. K. Shute and found normal. Not conscious; restless; pupils dilated; gnashing of teeth.

May 1. Restless and noisy; difficulty in breathing at times.

May 2. Death.

*Necropsy.*—Body of male white child, 3 years old. Section made sixteen hours after death. Brain showed marked venous congestion over vertex. There was an increase of serous fluid in the ventricles. Along the base there was a

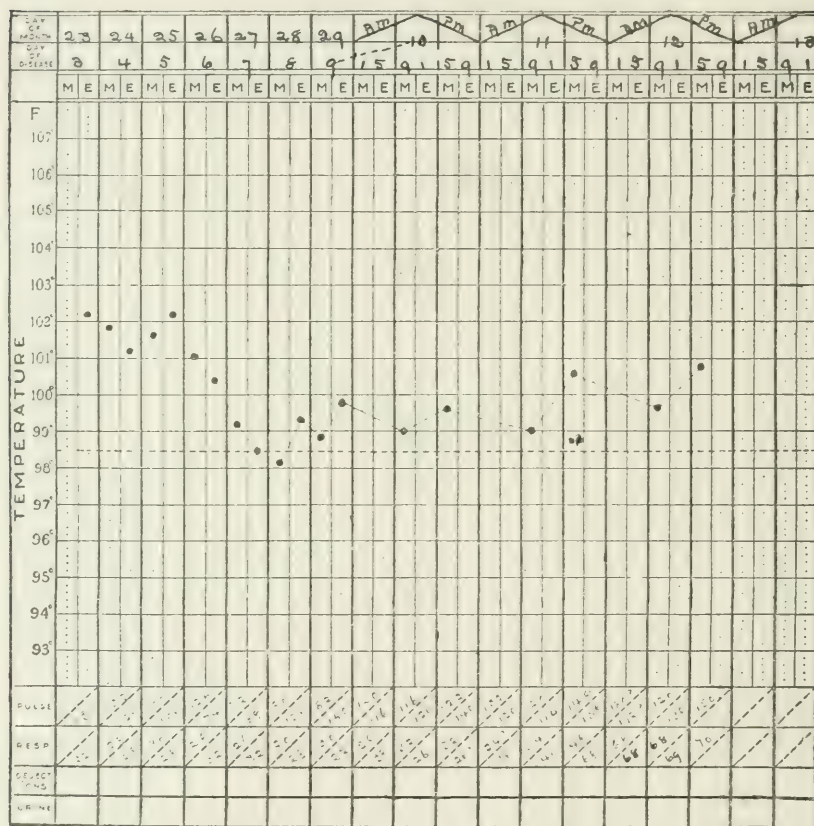


Chart giving data in author's Case 2.

meningitis with a formation of plaques of fibrin. The meningitis did not extend down the cord. On section the brain substance was found normal. Right kidney, stomach and intestines normal, though stomach showed some ptosis. Left kidney, spleen and pancreas showed marked relaxation of their attachments. Pancreas was flaccid and smaller than normal. Pericardium contained small amount of fluid. The lungs were congested and there was a subpleural effusion of blood at base of left lung. There were no areas of consolidation. Bronchial glands normal. No signs of tuberculosis. Mesenteric lymph-nodes enlarged.

*Anatomical Diagnosis.*—Basilar meningitis. (B. M. Randolph, pathologist.)

The following cases of meningitis complicating parotitis have been reported in young persons:

HARVEY LINDSLY: Two cases of death in brothers occurring a year apart, with similar symptoms. The ages are not given, but one was a student at Princeton College and the other a young medical student in this city. The fifth day after the onset of mumps there was persistent priapism in both cases, with delirium, restlessness, convulsions and death within two days. Post-mortem examination in the last case showed "Inflammation and congestion of the cerebellum, the cerebrum being normal."

MOURO AND HEALY: Male, 15 years of age, had mumps (temp. 107.2 F.) with recovery. Suddenly became delirious, hyperesthetic, with coma; maniacal outbreak; orchitis; for six months had difficulty in walking; paresis, and incoordination of legs; difficult speech and marked aphasia.

GLENCREAU: Girl 2½ years old; paralysis right side; convulsive movements at commencement. Recovery in some weeks.

Girl, aged 8 months; light convulsions shortly after the onset of mumps; died within twenty-four hours.

Boy, aged 4 years; extreme restlessness and convulsive movements with the onset of mumps; paralysis of left side.

Boy, aged 5 years. Violent delirium came four days after the onset of mumps. Restlessness with hallucinations. Recovery.

Boy, aged 10 years; severe convulsions with general insensibility; paralysis of left side; marked constipation and difficult micturition. These symptoms lasted a long time.

JOFFROY: Girl, 4½ years of age. The eighth day of mumps, sharp pains in arms and pruritis and afterwards pains in legs. Tendon reflexes and electrical reactions abolished. Hyperesthesia. There was a slight intermittent albuminuria; flaccid paralysis came on twenty-one days after the onset of the disease in the lower extremities and extended to the upper extremities about ten days afterwards. Bladder and rectum normal.

J. R. BROMWELL: Girl, 18 years of age; meningitis; death.

Boy, 11 years of age; four days after the onset of the disease had high fever, delirium, great pain in head, decided intolerance of light, nausea and vomiting. Temperature 104 F., pulse 120. In seven days the patient was well.

ELSAESSER: Three cases. Males from 9 to 11 years of age. Cheyne-Stokes respiration, vomiting, delirium, somnolence, speech disturbance, convulsions, paralysis, death.

COMBY: Boy, 10 years old, presented symptoms of tuberculosis, headache, vomiting, constipation, and rigidity of neck which came on eight days after mumps. Was well in a few days.

NOBÈCOURT AND BRELET: Girl, 12 years of age. On the third day of mumps there supervened headache, vertigo, vomiting, bradycardia, irregular pulse, pupils contracted, Kernig's sign, stiffness of neck and absence of patellar reflexes. At the acme of the disease lumbar puncture showed an abundant lymphocytosis of the clear cerebrospinal fluid which lasted a few days. After a few days the symptoms disappeared without leaving any trace except that the patellar reflexes were feeble for a long time, but became normal.

NETTER: Boy, 9 years old; violent pains in back, kidneys and limbs; Kernig's sign well marked; temperature 40 C. Twenty-four hours later both parotids were swollen. For several days there were brisk movements of the muscles of the face and left arm.

SALAMONSEU: Case 11 years of age. At the end of an attack of mumps there was chorea which lasted for six months and this was preceded by tetany.

J. W. FINDLEY: Female, 2 years of age, had mumps fourteen days. On the sixteenth day became paralyzed after convulsions. Left hemiplegia.



REVELLIOD: Boy, 7 years of age, had mumps with vomiting and fever. In a few days he was apparently well but was weak in left leg. Several weeks afterwards entered hospital; intelligence good; could not stand, rise or hold up head; paralysis of left side of face and eye. Facio-glosso-laryngeal paralysis; all extremities inert; patellar reflexes abolished. In three months recovery with exception of the patellar reflexes.

VAN DUYSE: Girl of 8 years; optic neuritis; violent headache. Later on vomiting and paresis of left side; speech difficult. Sight did not improve.

J. H. WOODWARD: Eleven-year-old child with neuro-retinitis.

BOYREAU: Boy, 11½ years old. February 6. General malaise and headache. Next day there was nausea, vomiting and epistaxis. Temperature 38.8 C., pulse 120. The left parotid became swollen and the following day the right one.

February 10. Could not get up; vomiting; pulse 80; less fever. The next day there was headache, vomiting, constipation, with irregularity of pupils and photophobia. Pulse 58 and irregular.

February 12. Vomiting continued. Pulse 48 and irregular. February 16. Child well.

HUTINEL: Girl, 10 years of age. Facial paralysis.

HEUBNER: Boy, 13 years of age. Psychosis; loss of memory; orchitis; recovery.

H. ZADE: Boy, 12 years of age. Vomiting, chill, slow pulse. Two days later parotitis. Intense headache and other symptoms of intracranial pressure developed. In ten days there was complete recovery.

A. STERN: Two cases of meningeal complications.

Girl, 8 years old. Diplopia due to paresis of the right internal muscle, showing a lesion of some of the fibers of the inferior branch of the third nerve.

Male, 16 years old. Bradycardia, pulse 30 to 38 per minute, headache, extreme dizziness, slight rigidity of the neck, vomiting, loss of appetite and nystagmus. Hearing poor in right ear.

F. L. BENHAM: Boy, 15 to 16 years of age. Mumps and orchitis. Temperature 104 F., pulse 120, vomiting, frontal headache, delirium, tâche cérébrale, stupor.

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A CASE OF CONGENITAL CYST OF THE THYROID  
GLAND, IN A CHILD AGED 1 YEAR, PRODUCING  
DEATH BY ASPHYXIATION \*

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Thyroid enlargements in this tropical portion of the world are met with more frequently in the white race than among the blacks.

During the past three and a half years, at the Board of Health Laboratories, Ancon, twenty-one specimens of thyroid glands showing large colloid cysts associated with hemorrhages and fetal adenomata have been received from the surgical clinic of Ancon Hospital, and four similar cases have been found at necropsy during the same interval of time. Sixteen of them occurred in females and nine in males. Thirteen of these cases were in Americans, all but one being females. Seven were in male Spaniards. One instance in a male Panamanian and one in a male Greek. Only three of the twenty-six cases occurred in negroes: two female Jamaicans and one female Barbadian. The ages range from 19 to 61 years, the average being about 38 years. A fair idea of race incidence at Ancon Hospital may be had from a recent analysis of 1,500 successive necropsies in which 1,088 were West Indian negroes, 230 Spanish-Indian mixture, 108 Spaniards, 25 Americans, the other 49 being divided among the various countries of the old world. Thus, one may form an idea as to the relative frequency of thyroid disease among the Spaniards and Americans and the low percentage in the black race.

Observers in Ceylon<sup>1</sup> and Africa state that goiters are not uncommon in the blacks of those regions. A search for the incidence of goitrous conditions in children almost proved fruitless.

Among 642 cases of goiter in children at Berne, where endemic goiter exists, Demme<sup>2</sup> found fifty-three in which the disease was congenital and a statement was added that the condition might cause severe dyspnea or even suffocation.

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\* Published with permission of the Chief Sanitary Officer, Colonel W. C. Gorgas, U. S. A.

1. Castellani and Chalmers: *Manual of Tropical Medicine*, p. 1025. William Wood & Company, N. Y., 1910.

2. Buck, A. H.: *Reference Handbook of the Medical Sciences*, iv, 381. William Wood & Company, N. Y.

According to Virchow<sup>3</sup> and Bednar, congenital goiter is not uncommonly associated with enlargement of the thymus gland. A prominent feature in this case.

Abt<sup>4</sup> (Chicago) observed a case of congenital goiter. The child died at birth with a tumor the size of a walnut which involved the entire gland.

At Ancon during the past three and a half years 130 children under 2 years of age have been subjected to an anatomical investigation and only in this one instance has a pathological condition in the thyroid been found, barring the exception of minor degrees of developmental variations in size, shape and location. The thymus gland has in several instances presented interesting features, but there was no associated change in the thyroid.

Ziegler<sup>5</sup> states that fetal adenomata of the thyroid gland are common and that hemorrhages are exceedingly apt to occur in glands possessing fetal adenomatous areas, cystic changes often developing as a sequel. Marine<sup>6</sup> supports this view.

#### CASE REPORT

*History.*—A brown female child, 1 year old and a native of the Republic of Panama.

*Family History.*—Father and mother living and in good health. Paternal grandmother and great grandmother living and in good health. History of maternal grandparents unknown. One brother, 7 years old, and one sister, 4 years old, in good health. Mother claims to have had no other children except these three and no miscarriages or abortions. She states that the delivery in each case was normal. No physician was ever present, a midwife having attended her. The immediate members of the family were examined and no unusual enlargement of the thyroid or any of the superficial gland sets was noted. Each member of the family shows a considerable degree of anemia; this is not unusual in persons of this class and locality. Other than this all were in good health. The mother and father both state that the child was born with a swollen neck, but that she had an uneventful babyhood and was never ill until twenty-eight hours before her death, when, about 4:30 a. m. she had what her mother thought was a "beginning attack of fever" with difficult breathing. The dyspnea became gradually worse during the day and following night, the child dying from suffocation early the following morning. There was no history of chills, convulsions or vomiting. A physician was not called until after the child's death.

*Examination.*—Attention was at once attracted by the tremendously swollen neck. The swelling extended from the point of the chin to the superior border of the sternum and laterally from the median line on either side. The first thought entertained was "diphtheria" with an extensive cellulitis. A mouth gag and tongue depressor were used to examine the throat and the structures were found normal except for a pale mucous membrane. The mass was then palpated and a cystic condition determined. An abscess was then considered, though there

3. Quoted, Buck's Reference Handbook of the Medical Sciences.

4. Quoted, Buck's Reference Handbook of the Medical Sciences.

5. Ziegler, E.: A Text-Book of Special Pathological Anatomy. The MacMillan Company, N. Y., 1898.

6. Marine, D., and Lenhart, C. H.: The Pathological Anatomy of the Human Thyroid Gland, Arch. Int. Med., 1911, vii. 506.

was not the inflammatory appearance of the skin usually found over the site of even a deep seated abscess. The tumor mass was punctured to ascertain the character of the fluid. Surprise was occasioned by the escape of a clear, watery, odorless fluid. After the content had been liberated the mass collapsed, and the structures under the skin, i. e., the trachea, larynx, etc., could be freely palpated and seemed normal.

The body was forwarded to the Board of Health Laboratory at Ancon for necropsy and pathological report.

*Anatomical Report.*—Autopsy number 3480. Date of death, May 8, 1913, at 4:30 a. m. Autopsy fifteen hours later. The body was that of a well-nourished but anemic-looking baby girl resembling the type usually spoken of as Spanish-Indian. Cutis anserina was very noticeable in the axillary, shoulder and inguinal regions. A large flabby tumor mass was found on the anterior surface of the neck in the median line and bulging to either side. It began at the level of the most prominent portion of the thyroid cartilages and extended downward almost to the sternum and clavicles. Laterally, its boundaries would have been well represented by the width of the neck. Over the center of the mass in the median line was found a small incised wound penetrating the skin and the cyst wall of the tumor mass. Pressure caused a little pink stained, clear, non-odorous, watery fluid to escape.

Cranium: Skull, brain, meninges all normal but for congestion. Middle ears, mastoids, etc., normal.

Eyes: Pale conjunctiva but no exophthalmos.

Nose, Mouth and Laryngo-Pharynx: Aside from pronounced degree of lymph-adenoid hyperplasia everything was quite normal.

Neck: The larynx was without any evidence of inflammatory disease and anatomically seemed normal. Beginning at the junction of the trachea and larynx and extending downward for almost 2 cm. there was marked stenosis of the trachea due to the flattening produced by compression of the tumor mass. There was no erosion, however, of the mucous lining in this portion of the trachea. All glands about the jaws and neck were large, firm, pink structures but showed no focal changes. Dissection of the cervical structures revealed the presence of all except the thyroid gland whose position was occupied by the collapsed tumor mass. No evidence of the thyroglossal duct could be found.

The large cystic tumor, when dissected free, measured 6 cm. in its vertical diameter, 6.5 cm. transverse diameter, and 2.5 cm. in an antero-posterior diameter. (These measurements, of course, were made on the empty tumor mass.) Its base was a thick fibrous mass with a few knob-like processes suggestive of thyroid tissue, while the rest was a large, thin, fibrous wall forming a huge compartment that had been partially divided by a fibrous partition arising from the base. Its general contour *in situ* was that of a large oval disk. At the lower posterior corner on the left, and the upper right posterior corner, were found two bodies which appeared to represent parathyroid bodies somewhat enlarged. Even when dissected free, the trachea still retained its flattened wall and a marked degree of stenosis.

Thorax: When the sternum was removed, a tremendous thymus body was found with a weight of 47 gm. Its measurements were 9 cm. vertical diameter, 9.5 cm. transverse diameter and 2 cm. in thickness at the center of the left lobe.

There was no tracheal nor bronchial compression due to the thymus gland. Its position was lower in the thorax than usual and the gland was applied over the pericardium and heart in such a way that only the most inferior border of the cardiac outline could be seen. Two thin ribbons of thymic tissue peeped above the level of the sternum. The gland was sprinkled with miliary hemorrhages and was a firm cellular structure. All glands of the chest were like those of the neck. Lungs, emphysematous and congested. A few miliary hemorrhages of the pleura. Bronchial tree negative for foreign bodies. Heart, moderate effusion into the pericardium. Valves all normal. No congenital defect found.



Abdomen: Peritoneum normal. The mesenteric, mesocolic and all other gland sets show marked hyperplasia. Stomach and pancreas normal.

Intestine: All Peyer's patches and lymphoid elements of both large and small bowel showed intense hyperplasia without congestion or ulceration.

Liver: Fatty metamorphosis more or less marked and a slight degree of post-mortem degeneration. Gall-bladder and ducts normal.

Spleen: Somewhat enlarged and solid. All the malpighian bodies showed an intense degree of hyperplasia. Kidneys and adrenal glands, normal. Pelvic organs normal. External genitalia normal.

Bone marrow of rib and femur dark red and cellular. Smears from the rib marrow, the spleen and brain were negative for malarial parasites or pigment.

The culture from the spleen was sterile, and the Wassermann test on the post mortem serum was negative (Dr. Bates).

Weight of Organs: Brain, 925 gm.; liver, 315 gm.; right lung, 80 gm.; left lung, 60 gm.; kidneys (combined), 55 gm.; spleen, 35 gm.; heart, 40 gm.; thymus gland, 47 gm.

Weight of empty thyroid cyst, 35 gm.

*Microscopic Examination.*—Thyroid gland: Sections from the base of the tumor taken from either side of the tracheal groove showed a picture somewhat resembling fetal adenoma, but there were a moderate number of irregular large acini containing colloid and they have a distorted wall with narrow epithelial lining. The stroma was increased in amount. Sections taken from the zone in the base near the cyst wall showed larger acini fairly well filled with colloid and even here the stroma was thickened. Sections from the base of the cyst wall showed a tremendous fibrous stroma which had almost closed the acini and only desquamated cells were found in them. Here and there a long hemorrhagic area appeared. The cyst wall was a dense, fibrous structure.

Parathyroids: The suspected bodies proved on microscopic examination to be accessory thyroids.

Thymus Gland: A very extensive, fine, lymphoid hyperplasia with multiple hemorrhages usually in a subcapsular position.

Lymphatic Nodes: Extensive hyperplasia. Germinal follicles greatly enlarged.

Spleen: Hyperplasia of the malpighian bodies, marked. The centers of the malpighian bodies as well as the centers of the germinal follicles in the lymph-nodes were filled with large vesicular and epithelioid cells, while the small lymphoid cells were packed about them in a very compact zone. An occasional malpighian body and germinal follicle showed a point suggestive of necrosis without leukocytic infiltration.

Intestine: All lymphoid collections showed extensive hyperplasia.

Lungs: All the alveoli were distended and in many places ruptured. Infrequent areas of atelectasis were also found.

Liver: Injected. A moderate periportal cirrhosis existed and there were numerous small foci of connective tissue cells occupying, evidently, the site of necrosis.

Kidneys, adrenals and brain were intensely injected.

Pancreas: Moderate post mortem degeneration.

The case would appear to represent a congenital cyst of the thyroid. The origin of the cyst is probably explained by Ziegler, as a fetal adenoma of the gland with hemorrhagic and cystic changes resulting in its neighborhood. Injury to the gland during labor may also be open to consideration as having been a factor in the causation of the cyst. A second point of interest is the marked degree of lymphatism found in fatal association with the thyroid cyst. Observations on surgical specimens and the autopsy series would indicate a low incidence for goiter in the black race of the West Indies.

# PROGRESS IN PEDIATRICS

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## A REVIEW OF RECENT WORK ON MEASLES

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There have been several important contributions of late on measles which have brought out several very important points relating to its immunity problems. Much still remains to be done, however, in solving the immunity problems connected with measles.

Experimentally, the work on measles dates back to 1852, when Mayr was able to prove that nasal and buccal secretions from patients suffering from measles were infective.

In 1898 Chavigny first reported the appearance of what he considered to be measles in a monkey which had come into close contact with his keeper while he was in the early stages of an attack of measles.

Josias, in 1898, stimulated by Chavigny's report, allowed monkeys to play in a measles ward without any effect.

In 1905 Hektoen did some experimental work with measles, injecting the blood from a human case during the early eruptive period into man successfully.

In 1910 Anderson and Goldberger reproduced measles in monkeys, and carried it through at least six generations, showing that the virus can retain its pathogenicity for a considerable length of time.

Lucas and Prizer were able to repeat the observations of Anderson and Goldberger, and demonstrate not only the typical temperature rise and rash, but observed Koplik spots with the typical blood-picture.

From these combined researches it can be concluded that the *Macacus rhesus* monkey is susceptible to a mild kind of measles if injected with the virus of human measles, that the virus is present in the blood-serum at some time at least twenty-four hours before the appearance of Koplik spots, and that the virus remains in a virulent form in the blood at least thirty-six hours after the appearance of the skin eruption. These researches have brought out the fact that in the pre-eruptive stage of the disease there is a certain definite blood-picture. This phase of the subject has been worked up most extensively by Hecker.<sup>1</sup>

All experimental work has shown that the prodromal or pre-eruptive stage is the most infectious period of measles. Hecker has made a careful

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1. Hecker, R.: Cytological and Clinical Observations During Measles Incubation, *Ztschr. f. Kinderh.*, May, 1911.

study of the blood during this period, and on account of the importance of this work, I have practically made a complete translation of his article, which follows:

CYTOLOGICAL AND CLINICAL OBSERVATIONS DURING THE INCUBATION PERIOD OF MEASLES, BY R. HECKER

In certain acute infections, such as scarlet fever, measles, variola, vaccine, typhus, etc., there is a typical course, in which the reaction between the infecting virus and the forces of the organism contending against it flows off under certain determined forms which we can register exteriorly as temperature, changes in the skin, swelling of organs, fluctuation of weight, etc. In regard to the processes which go on internally, we seek to advance sometimes through anatomical means, sometimes through biological investigations. We see how at certain periods a disease is also determined, and how in every case recurring changes in the internal conditions of the body follow. So in blood-serum follows the formation of different antibodies, complement fluctuations, etc., and on morphological elements follow changes in the blood, numerous displacements, and the beginning of new forms; or we determine directly the connection between virus and the protective power of the body (anaphylatoxin, phagocytosis, etc.). But on the whole our knowledge of the complicated inner processes in acute infections is still deficient. In particular we know very little on the question of the time between the entrance of the virus and the breaking out of the disease, that is, the incubation period, although we must assume that lively changes, indeed, positive revolutions take place in the body at these times, and although the duration of this time of preparation in any disease has been well known to us for a long time.

So each new fact which we are able to learn as bearing on the typical changes in the matter of any determined infectious disease can itself be of significance for the body or knowledge regarding the given disease, it also has the same significance for the investigation of the biological beginnings in other diseases. Further than this, we can also expect through the study of the incubation times, continuous development of data for an earlier diagnosis.

Of importance also is a better clinical observation of incubation, and before all else, the study of the changes in the blood rather than of any single organ which is accessible *in vivo*, or an anatomical investigation.

The consideration of the blood changes has up to now yielded the results that in lobar-pneumonia as in epidemic cerebrospinal meningitis and influenza, increase of white blood-corpuscles (leukocytosis) takes place, while typhus abdominalis and measles are distinguished by a lessening of leukocytes (leukopenia). In pneumonia and meningitis, among the leukocytes, polynuclear neutrophil cells are specially increased,



while lymphocytes are diminished. In typhus, there appears to be chiefly a diminution of pleomorphic nuclear cells, while lymphocytes are equally increased. For anything more exact on the subject of the upward or downward motion of single cell forms during the acute stage of diphtheria, scarlet fever, typhus, erysipelas and pneumonia, we have to thank the investigations of Ziegler and Schlecht.

The special findings with regard to measles all give one account of how the eruption proceeds. In opposition to Haymen, who speaks of an increase of leukocytes, all other observers (Pee, Rieder, Felsenthal, Sobotka, Turk, Combe, Rechzeh, Sperk, Neumark) agree decidedly that there is a plain diminution of leukocytes at the height of the disease. And Rieder pointed out in 1892 the diagnostic bearing of this leukopenia in respect to scarlet fever.

The diminution of leukocytes during the period of eruption is related in substance to the lymphocytes according to the findings of Turk, Rechzeh and Erben. No doubt exists any longer that during the eruption the eosinophil cells are diminished, indeed disappear entirely out of the blood (Zappert, Felsenthal, Rechzeh, Erben).

During the incubation stage, Sobotka found as did Combe and later Tiliston, a leukocytosis, which shortly before the eruption gave way to a leukopenia. According to Combe, leukopenia begins two days before the eruption; according to Tiliston, leukocytosis reaches its height six days before the eruption, and after that decreases. Combe believes that not the lymphocytes but the polymorphous cells disappear.

In a study no further carried out, Sperk finds that leukopenia is present not only during the eruption, but often also as a prodromal symptom.

Differential counts of single cell formation during the incubation period, specially of lymphocytes and neutrophils, have not been done up to now.

With regard to the relation of mononuclear to polynuclear neutrophils, Flesch and Schossberger have conducted investigations, with the result that not only in the efflorescent but in the incubation stage of measles there is a decided displacement of neutrophil blood formation on the left side, according to Arneth's formula, and further, that the count of mononuclear cells increases greatly in contrast to the polynuclears. Flesch and Schlossberger saw this displacement begin about six to seven days before the appearance of Koplik spots, and reach their height about three to four days before this symptom.

The findings with regard to measles incubation, so contradictory and few, induced me over a year and a half ago to investigate this period of measles. At the Salzburg Congress in 1909 I studied three pairs of brothers and sisters in whose cases a decided diminution of leukocytes and further diminution of lymphocytes had shown itself. These



researches were set forth and a statement of the same conditions given out in respect to six more children.<sup>2</sup>

Ludwig studied blood formation in the cases of two children of the same family who had measles, in a work undertaken at my direction, and confirmed my findings with regard to the lessening of leukocytes and lymphocytes during incubation. I now am working on the cases of fourteen children, among them five sets from one family, whose blood was taken during the incubation time.

In the cases of the first six children the leukocytes were only reckoned by counting the field of vision. This method is certainly not a complete one, and under some circumstances can easily be productive of deceptive results. Yet with certain precautions, it yields, in the hands of a careful observer, exceedingly useful results. I have, for purposes of clearness, noted only three ways of marking: Normal (L. N.), leukopenic (L. P.) and leukocytosis (Lkts.). By this means, the limits of the normal show so clearly that what is marked as leukopenic or leukocytosis, corresponded actually to a definite decrease or increase of white blood-cells. In one case (Gisela S.) a very accurate count was taken, while in one control case, in which the absolute leukocytic count was made, the count in the field of vision was also made, and this then compared with the field of vision of the preparation to be reckoned. The findings reached by this primitive method — leukopenia and eosinopenia — were verified in later cases with an exact count.

In the counting, on an average, there were 350 single cells, distributed among lymphocytes, neutrophils, eosinophils, large mononuclears and transitional cells, as well as disintegrated cells. Mast cells and plasma cells appeared at times, but need not be recorded here as they showed nothing typical.

#### BLOOD FORMATION IN SEPARATE CASES

The children ranged in age from 13¼ years to 9 years, and were all healthy up to this time; some of them were delicate, but none dyspeptic (Tables 1 to 12).

TABLE 1.—DIFFERENTIAL BLOOD-COUNT IN FRITZ U., AGED 6

Date* Nov.	Lympho- cytes	Neutro- phils	Large Mono. and Trans.	Eosin- ophils	Disin- tegrated	Total
11	26.8	55.7	8.5	....	10.7	4.200
12	39.0	46.2	7.8	....	7.2	2.400

\* On 11, coughing; 13, koplik sign; 14, eruption began; 15, eruption spreading.

2. Hecker, R.: München. med. Wchnschr., 1910, No. 30.

TABLE 2.—DIFFERENTIAL BLOOD-COUNT IN VERA H., AGED 5

Date	Lymphocytes	Neutrophils	Large Mono. and Trans.	Eosinophils	Disintegrated	Total
16	59.1	32.4	4.9	0.9	2.2	7,800
17	50.4	38.8	5.1	1.2	4.8	7,900
18	57.6	34.5	1.2	1.8	6.0	10,600
19	51.8	35.3	1.0	0.7	10.3	6,500
21	29.2	64.2	4.2	....	1.6	9,100
22	25.1	61.1	5.4	....	7.8	7,000
23	47.4	43.4	5.4	0.4	3.1	6,100

TABLE 3.—DIFFERENTIAL BLOOD-COUNT IN GISELA S., AGED 1 $\frac{3}{4}$ , WITH POLIOMYELITIS

Date	Lymphocytes	Neutrophils	Large Mono. and Trans.	Eosinophils	Disintegrated	Total
20	58.5	31.5	2.2	....	7.8	10,000
21	62.6	26.4	6.0	....	4.8	13,000
22	54.0	39.9	6.1	0.2	10.0	10,000
23	47.6	39.1	6.2	....	7.2	5,000
24	39.2	44.0	6.1	....	10.7	5,000
25	32.8	49.0	5.2	0.2	12.6	3,000
26	38.6	50.2	4.6	....	6.5	4,000
27	53.0	42.6	1.7	0.1	2.2	9,000
28	37.1	52.9	2.4	....	8.0	45,000
29	39.5	53.8	3.0	0.8	3.0	8,000

TABLE 4.—DIFFERENTIAL BLOOD-COUNT IN IDDY H., AGED 2 $\frac{1}{2}$ 

Date*	Lymphocytes	Neutrophils	Large Mono. and Trans.	Eosinophils	Disintegrated	Total
13	69.2	22.5	2.4	0.9	4.0	9,800
15	62.7	28.4	4.1	1.9	2.4	9,400
17	66.2	30.9	0.3	1.6	0.8	6,500
20	....	....	....	....	....	7,900
21	....	....	....	....	....	6,050

\* On 21, restlessness; 22 and 23, conjunctivitis; 24, outbreak of eruption. Outbreak of eruption on her sister.

TABLE 5.—DIFFERENTIAL BLOOD-COUNT IN CAROLA E., AGED 3

Date*	Lymphocytes	Neutrophils	Large Mono. and Trans.	Eosinophils	Disintegrated	Total
15	30.6	55.0	3.1	6.5	4.6	5,200
16	40.9	49.4	2.6	1.6	7.0	5,000

\* On 16, Koplik sign plainly shown; 17, beginning of eruption; highest temperature, 38.2.

TABLE 6.—DIFFERENTIAL BLOOD-COUNT IN KLEMENS E., AGED 4.

Date*	Lymphocytes	Neutrophils	Large Mono. and Trans.	Eosinophils	Disintegrated	Total
15	41.9	39.4	2.4	0.2	5.6	11,000
16	42.6	47.3	0.4	0.2	9.8	7,700

\* On 16, Koplik sign; 17, full outbreak on whole body; highest temperature, 37.9 C.

TABLE 7.—DIFFERENTIAL BLOOD-COUNT IN ERIK C., AGED 7

Date*	Lymphocytes	Neutrophils	Large Mono. and Trans.	Eosinophils	Disintegrated	Total
5	35.4	48.3	8.1	2.0	5.9	12,600
7	45.7	50.7	0.6	2.1	0.4	10,000
10	41.4	49.9	3.5	0.3	4.5	.....

\* On 5, coughing, dizziness, shivering, weariness, and red eyes; 6, benefit received from medicine; 7, coughing, pallor, no Koplik spots; 8, in evening eruption began; 9, eruption spreading; 10, fever; no great attack on whole body.

TABLE 8.—DIFFERENTIAL BLOOD-COUNT IN HUGO C., AGED 5

Date*	Lymphocytes	Neutrophils	Large Mono. and Trans.	Eosinophils	Disintegrated	Total
5	44.7	45.7	3.2	4.9	1.1	14,600
10	47.3	33.7	4.9	5.0	8.7	.....
12	45.4	40.2	6.5	6.2	1.3	17,300
17	41.1	49.5	3.3	2.9	3.0	9,200
18	40.8	53.1	3.0	....	3.0	8,400
19	45.0	47.4	3.0	1.3	3.1	7,100

\* On 12, conjunctivitis; 18, fever, no Koplik spots, no coughing; 20, dizziness. reddening of gums, no coughing; 21, spreading of eruption, coughing at night, some Koplik spots.

TABLE 9.—DIFFERENTIAL BLOOD-COUNT IN MARIE SP., AGED 4

Date*	Lymphocytes	Neutrophils	Large Mono. and Trans.	Eosinophils	Disintegrated	Total
7	34.7	54.4	3.3	4.3	0.3	Lets.
10	45.3	47.6	1.4	....	5.7	Lp.
11	31.6	65.5	1.5	0.2	1.2	Lp.
14	57.7	31.9	6.0	0.6	4.1	Lp.
17	29.7	64.6	1.5	0.7	3.2	Lets.
23	42.4	47.5	4.2	0.5	4.9	No.

\* On 7, reddening of buccal mucous membrane; 10 Koplik spots; 13, outbreak of eruption; 14, eruption faded.

TABLE 10.—DIFFERENTIAL BLOOD-COUNT IN ANNA SP., AGED 3

Date*	Lympho- cytes	Neutro- phils	Large Mono. and Trans.	Eosin- ophils	Disin- tegrated	Total
7	50.8	21.6	5.0	4.1	18.3	Lp.
10	48.9	47.4	1.0	1.0	2.2	N.
11	30.8	62.7	3.2	....	5.0	Lp.
14	37.8	57.7	0.7	....	3.4	Lp.
17	39.2	57.2	1.8	1.7	0.5	Lets.
23	39.5	50.0	2.8	....	7.7	Lets.

\* On 10, Koplik signs, reddening; 13, eruption began; 15, eruption fading.

TABLE 11.—DIFFERENTIAL BLOOD-COUNT IN CLARA B., AGED 8

Date*	Lympho- cytes	Neutro- phils	Large Mono. and Trans.	Eosin- ophils	Disin- tegrated	Total
9	60.2	37.9	0.3	1.6	....	Lets.
12	45.8	44.9	5.2	4.0	0.3	Lets.
14	33.4	54.7	6.8	0.3	5.0	Lp.

\* On 15, Koplik sign; 17, eruption.

TABLE 12.—DIFFERENTIAL BLOOD-COUNT IN IRENE B., AGED 9

Date*	Lympho- cytes	Neutro- phils	Large Mono. and Trans.	Eosin- ophils	Disin- tegrated	Total
6	32.2	56.7	7.9	1.0	1.7	N.
12	23.0	72.3	2.4	1.8	0.6	N.

\* On 10, Koplik signs; 12, eruption began.

In the following tabulations I have arranged all cases from the day of the outbreak of the eruption so as to give at one glance the changes in the blood throughout the period. The appearance of Koplik's spots was particularly noted.

#### THE GREAT QUANTITY OF LEUKOCYTES

In the accompanying tabulation it is shown that all the cases show a definite decrease of leukocytes not only during the acute stage, but also during incubation. At times, leukopenia was decided, even as many as 2,400; at times only relatively so, that is, a decrease in contrast to the earlier leukocytosis, of a nearly normal count.

The period of duration of this leukopenia was determined in a series of cases. It was indeed already evident.



2 times 1 day before outbreak of the eruption.  
 3 times 2 days before outbreak of the eruption.  
 3 times 3 days before outbreak of the eruption.  
 2 times 4 days before outbreak of the eruption.  
 2 times 7 days before outbreak of the eruption.  
 1 time 8 days before outbreak of the eruption.  
 Averaging 3 times 6 days before outbreak of the eruption.

Its first coming on was noticed:

2 times 1 day before outbreak of eruption.  
 1 time 3 days before outbreak of eruption.  
 1 time 4 days before outbreak of eruption.  
 2 times 7 days before outbreak of eruption.  
 1 time 8 days before outbreak of eruption.  
 Averaging 4 times 4 days before outbreak of eruption.

Before the Koplik spots or leukopenia was evident,

2 times 0 days.  
 1 time 1 day.  
 1 time 3 days.  
 1 time 5 days.  
 1 time 6 days.  
 1 time 8 days.  
 Averaging 3 times 3 days.

Leukopenia was generally continuous, but there were certain fluctuations in the leukocyte count, specially around the third day before the breaking out of the eruption, which one could regard as showing only relative leukocytosis. In two cases (Clemens and Erik) there was decided leukocytosis still two days before the eruption. In two other children it was noticed six days before, and with one other eight and in one nine days before.

Without doubt, leukopenia appears as a typical blood change during the last day of incubation. Its presence in suspected cases can be allowed to have a direct bearing on the diagnosis.

Whether leukocytosis during the first half of the incubation period and around the third day before the outbreak of the eruption is a constant phenomenon, neither my observations nor those of Combe show. According to Combe's researches, initial leukocytosis plainly exists as a rule. Yet further investigations on this question are necessary.

With regard to the persistence of leukopenia during the later stages of the diseases, I judge from the results in the cases of the sisters Hildegard and Ingeborg that from five to nine days after the beginning of the eruption decided leukopenia is present. In the case of Ingeborg, evident leukocytosis started in on the seventh day after the eruption.

#### LYMPHOCYTES AND NEUTROPHILS

In order to give a basis for understanding the following tabulations, I place here the statements of Japha, Lazarus, Karnisky and Carstanjen

with regard to the percentage share of single cell forms in the blood formation.

## JAPHA

	Newborn	Sucklings	Grown
Leukocytes . . . . .	20,000 u. m.	12-13,000	8,000
Lymphocytes . . . .	20 per cent.	50-55 per cent.	34 per cent.
Polynuclears . . . .	70 per cent.	25-30 per cent.	ea. 60 per cent.
Eosinophils . . . . .	2 per cent.	2- 7 per cent.	2 per cent.
Monos. and transitionals..	8 per cent.	8-15 per cent.	4 per cent.

## LAZARUS

Lymphocytes . . . . .	22-25 per cent.
Large Monos. and transitionals. . . . .	2- 4 per cent.
Polynuclear neutrophils . . . . .	70-72 per cent.
Eosinophils . . . . .	2- 4 per cent.

## KARNISKY

	Bis 4 years	4-8 years	8-15 years
Lymphocytes . . . . .	52% (54-49)	42% (44-41)	30-34%
Neutrophils . . . . .	35% (34-48)	46% (47-46)	52-55%
Large Monos. and transitionals . . . . .		11.5-4.2%	
Eosinophils . . . . .		12.5-0.7%	..

## CARSTANJEN

	2 years	3 years	4 years	5 years	Later
Lymphocytes ...	47.0% (42.8-50.2)	38.4% (33.2-43.0)	33.4% (22.8-43.2)	25.1% (18.5-36.0)	25.1-33.2%
Neutrophils ....	41.9% (38.4-43.9)	48.2% (42.9-52.7)	52.6% (44.6-60.0)	60.9% (46.1-79.0)	51.8-62.8%

In the foregoing tabulation the relation of lymphocytes to neutrophils (computed on the entire count of leukocytes) is expressed in a fraction of which the numerator is lymphocytes and the denominator neutrophils. The table yields a surprising and uniform result; during the first part of the incubation lymphocytes are absolutely in the majority; in the second half this relation is reversed, and either from one day to the next or with the great difference in the attack from two or three days; while both counts approach each other in value. This reversal of the relation with the displacing of the lymphocytes happens in all cases a number of days before the eruption, and before the appearance of Koplik's spots. Only one case was an exception (Hilda).

The exact time of the commencement of this phenomenon of reversal we can understand more accurately the longer the cases are observed at the beginning. The reversal is observable as beginning

1 time 4 days before the eruption.  
1 time 5 days before the eruption.  
1 time 6 days before the eruption.  
1 time 9 days before the eruption.

On an average of 6 days before the eruption.

The reversal was certainly accomplished

1 time	0	days before eruption.
3 times	2	days before eruption.
4 times	3	days before eruption.
1 time	4	days before eruption.
3 times	5	days before eruption.
1 time	9	days before eruption.

On an average of 3.8 days before eruption.

The latest limit was three days before eruption.

Let us take the appearance of Koplik's spots as a definite limit and then we see that the reversal takes place

1 time	exactly with Koplik's spots.
3 times	3 days before Koplik's spots.
1 time	4 days before Koplik's spots.
2 times	5 days before Koplik's spots.
1 time	9 days before Koplik's spots.

On an average of 4 days before Koplik's spots.

The earliest limit was nine days, the latest none.

The ratio of both cell forms is in this table arranged in columns in order to show the values of a single kind of cell, not on the basis of the whole count of leukocytes, but on the basis of the sum of lymphocytes and neutrophils, so that the ratio of both may be more clearly represented.

What does this displacement of the percentage count mean with reference to the real strength of the count of both forms? One would conclude that it might be entirely false, from the diminution of the relative lymphocyte count to a disappearance of lymphocytes. The displacement referred to can proceed from a decrease of lymphocytes or an increase of neutrophils; but it can also at the same time be a decrease or increase of both elements, with an outweighing disappearance of lymphocytes or an outweighing increase of neutrophils. From the foregoing it does not appear in the relative count which case is really the true one. If one had at the same time taken beforehand a reckoning of the total leukocytic cells in cubic millimeters, and from this got an absolute count, then the foregoing question could be simply answered on the basis of the relation of this count. This I must assert positively in opposition to Zangemeister and Gans, and I have already expressed myself more fully on the subject elsewhere.<sup>3</sup> Next, one can establish the real ratio by the count already made. If the relation of lymphocytes to neutrophils has involved a displacement in disfavor of the former in the taking of the total leukocytic count, as follows:

	Total Leukocytes	Lymphocytes Per Cent.	Neutrophils Per Cent.
First Count .....	17,000	58	36
Second Count .....	8,400	22	70

then only either a decrease of lymphocytes alone or of both elements can be admitted, considering the outweighing share of lymphocytes. If

3. Hecker, R.: München. med. Wehnschr., 1910, No. 48.

an increase of neutrophils alone or else of both forms is taken as the cause of the percentage displacement, then something new must be worked out necessarily; the total leukocytic count must be found increased.

But something more accurate may be established if one computes the absolute value of both kinds of cells:

If S equals total leukocytic count  
 l equals percentage lymphocytic count  
 h equals percentage neutrophil count  
 x equals absolute lymphocytic count  
 y equals absolute neutrophil count

Then we have the equation:

$$x:s = l:100$$

$$y:s = n:100$$

$$X = \frac{s \times l}{100} = \frac{17000 \times 58}{100} = 9860$$

$$Y = \frac{s \times n}{100} = \frac{17000 \times 36}{100} = 6120$$

1. Count of lymphocytes = 9860.  
 Count of neutrophils = 6120.
2. Count of lymphocytes = 1848 (computed from the last equation).  
 Count of neutrophils = 5880.

Between the counts in 1 and 2 there is also a fusion of both cell formations with a strong preponderance of lymphocytes: they have lost 63 per cent. of their quantity, the neutrophils only 47 per cent.

#### ABSOLUTE VALUE OF LYMPHOCYTES AND NEUTROPHILS

According to the first observations, where only the leukocytic count was taken, I had reached the conclusion that the lymphocytes are very definitely reduced and through their disappearance bring about a leukopenia. But a more exact observation was possible with the later cases.

One sees that the fact shows an absolute dying away of lymphocytes, which is also accompanied by some loss of neutrophils; but the decrease of the latter is never so great as of the former. There is a preponderance of lymphocytes.

#### RELATION OF LYMPHOCYTES AND NEUTROPHILS

The sum of both is fixed at 100 per cent.

The percentage loss may amount to:

	In Lymphocytes Per Cent.	In Neutrophils Per Cent.
In the case of Hugo .....	59	52
In the case of Vera .....	53	27
In the case of Gisela .....	89	62

In the case of the last child, the final effect was a sudden neutrophilcytosis at the end of the incubation; the decrease of lymphocytes 61 per cent., the increase of neutrophils 7 per cent.



The decrease of lymphocytes with three children in the first series of observations (taken without absolute leukocytic count) came to a sudden end at the same time that fever stopped, when a quicker motion began in the blood formation. The lymphocytosis now begun is only a seeming one; in reality, it was a neutrophilopenia, which springs out of the continuation and strengthening of the leukopenia. With one child the poverty of lymphocytes continued well into the convalescence.

The decrease of lymphocytes goes on either continually or one sees from one to two days before the eruption an intermittent rise at the same time with the rise of the total of leukocytes. The disappearance of neutrophils follows continually in the same manner as in the case of lymphocytes. Vera's case is worthy of remark, for in it during the same time that a disappearance of lymphocytes took place a not inconsiderable increase of neutrophils took place.

In the first half of incubation we see, corresponding as a rule with leukocytosis, also a rise of both cell forms.

The earlier view given out by me, that the decrease of lymphocytes is not an apparent one, somewhat due to the increase of neutrophils, but a real lymphocytopenia, is entirely in accord with this further finding that the neutrophils next are diminished, only in far smaller quantities. Typical, however, for the second half of measles, incubation is the reversal of the percentage relation between lymphocytes and neutrophils to the disfavor of the former.

#### THE NEUTROPHIL BLOOD FORMATION

The consideration of the neutrophil blood formation with the nuclear count as criterion which Arneth inaugurated, has certain dangers in it, since the judgment with regard to it, whether a cell has 1, 2, 3 or 4 nuclei, is often entirely dependent on the subjective conjecture of the investigator. Yet the method has confirmed itself as useful, and Arneth's declaration, that a certain standard shows itself in the distribution of neutrophil polymorphonuclear cells after the count of their nuclei under determined conditions, was also established by another investigator. So the growth of mononuclear neutrophils, found by Arneth to be relative in most infectious diseases (in part also absolute), was verified by Brugsch. With the blood formation in children who have infectious diseases, Flesch and Schlossberger have occupied themselves particularly and give out the following counts as normal:

1 Nucleus	2 Nuclei	3 Nuclei	4 Nuclei
36	45	15	3

They have, as already mentioned, especially in the case of measles, established that there is an increase of a few differentiated mononuclear neutrophils to the disfavor of polynuclear ones, not only in the efflorescent

stage, but also already toward the end of the incubation, beginning six or seven days before the coming out of Koplik's spots.

In my investigations the spider thread-like bridges between the nuclear fragments were not kept in mind; they were clearly artefacts of fixation (Turk, Grawitz). One cell with two fragments bound together by the most vaporous of bridges was counted as two nuclei. In the beginning of my observations I thought such a displacement of blood formation on the left side was clear during the eruption stage, but not to be taken as so during the incubation stage; I proved on the contrary in the cases of two children observed in the last days before the eruption that a real displacement occurred on the right side so that the three or four nuclear cells showed an increase.

Ludwig found, in the two cases studied by him during the last four or five days of the incubation, a decided increase of mononuclears and decrease of 3-nuclear neutrophils. I must to-day correct my earlier view on the basis of these and my own later observations, and after further revision of the first cases.

That the displacement in blood formation clearly is expressed in the count of mononuclear neutrophils, is the one truth I will subscribe to.

The following tabulation leaves no doubt that at the end of the incubation time in all cases there has taken place a percentage increase of mononuclear neutrophils, also a displacement on the left side.

In the analysis of the separate cases, one sees in the case of the two sisters Ingeborg and Hilda, observed throughout the whole incubation period, that the displacement started first one day before and in one of them simultaneously with Koplik's spots; in the remaining time, in contrast to the beginning, a relative decrease of mononuclears was remarked which in both cases was interrupted eight or nine days before the eruption by an increase.

The exact time of the coming on of the displacement we can determine in Cases 2, 3, 4, 9, 10, 11, 12, 13, 14. With these the displacement certainly begins on the left.

	1 time	with outbreak of eruption.
	2 times	2 days before outbreak of eruption.
	3 times	3 days before outbreak of eruption.
	1 time	5 days before outbreak of eruption.
	1 time	6 days before outbreak of eruption.
	1 time	7 days before outbreak of eruption.
	1 time	8 days before outbreak of eruption.
Or on an average of	4	days before outbreak of eruption.

Commonly a plain connection shows between the curve of the total neutrophils and the mononuclears. The question now arises whether the visible relative increase of mononuclear cells corresponds with a fixed numerical relation of mononuclear cells. The same relation is true here as between lymphocytes and neutrophils, namely, that the relative

increase of mononuclears has its origin either in a decrease of polynuclears or in an unequal increase or decrease of both cell forms. A decision on this would be reached through taking the absolute count. Such a calculation would only be possible where the absolute leukocytic count had been taken. And in these cases it appears that the relative increase in only three cases showed an absolute increase of mononuclears while in the other cases just the opposite was true. Here the displacement on the left also sprang from a decrease of polynuclears.

In spite of the fact that this displacement of blood formation on the left side is a constant occurrence in our cases, it means nothing characteristic regarding the real development of cell values.

Whether this displacement on the left is characteristic for measles must at present remain undetermined. According to Flesch and Schlossberger quantitative division appears in the acute stage of different diseases, but our view with reference to a fixed neutrophil blood formation is not determined in the case of any special sickness.

#### EOSINOPHIL CELLS

In my cases I also find as a rule the decrease already referred to on another page, of eosinophil cells, during the eruption stage, which amounts usually to an entire disappearance. The counts taken during the incubation time show a decided decrease, yet it is not always true that the disappearance of eosinophils has taken place already many days before the eruption. The decrease of eosinophils was determined as follows:

	2 times 1	day	before eruption.
	2 times 2	days	before eruption.
	4 times 3	days	before eruption.
	1 time 4	days	before eruption.
	1 time 7	days	before eruption.
On an average		2.9	days before eruption.

#### DISINTEGRATED CELLS

Besides the white blood-cells one finds — not considering erythrocytes and blood-disks — still other cell forms and structures which are from their formation to be characterized doubtless as disintegrating leukocytes.

Among disintegrated cells, I class all transitions from cells with indistinct nuclei to the cells formed of shreds of protoplasm and nuclear fragments, which remain before entire dissolution. Their size varies, but most of them are larger than healthy leukocytes. In coloring all degrees of difference are to be seen. Nuclei that still hold together are colored faintly like protoplasm. With further disintegration the distinct nuclear color disappears, and the whole structure appears diffusely tinged with the color of protoplasm (with eosin-methylene blue red; with azure more bluish). The coloring is often so pale that one can see plainly the erythrocytes underneath. Eosinophil granulations hold the color best.

In the formation naturally the most different gradations are noticeable; round, oval, polygonal besides blurred forms torn in strips and threads; many cells show their granulations floating off; so, except with the eosinophils, the surrounding sarcolemma does not appear so plainly.

The differentiation of disintegrated cells from their original form is only traceable a certain distance. The nuclei of neutrophils, except fractional ones, are often readily recognizable at the first step of decay, as is true of the eosinophil granulations; more difficult to determine are the lymphocytes; in Giemsa preparations they appear as red colored polygonal bodies without any visible protoplasm. But I can say as yet nothing positive on this point.

In German literature there is not much on these forms, but they appear to be identical with the disintegrated cells of Uskow, the solution forms of Botkin and the shadow-cells of Klein.

A priori it would seem that these disintegrated cells offer a directly opposite relation in their count to the count of leukocytes or other cell forms. The more the countable leukocytes disappear the more one can compute the disintegrated cells. But it has not yet been proved. In many cases the described relation is plainly observable, as in Hugo's case, or on a certain day in Vera's case, also with Carola and Klemens. With other children it was measured wrong.

This deficiency is not hard to understand. When a kind of cell is reduced in the blood formation, this will beyond all doubt be the evidence of a disintegration having taken place. But it is not entirely plain that this disintegration within the blood-vessels gets into the circulation; it is far more probable that it happens in larger measure within the organs. Further, with regard to the cells which dissolve in the circulation, it is in no way established how long they take to dissolve. So we may believe that cells or fragments of cells which proceed from an extensive breaking up of leukocytes remain in the blood only until the leukocytes have again increased through a regeneration or attraction of cells from their stores. So we have the total figure of disintegrated cells exactly correlated with the higher leukocytic count.

A diagnostic explanation for disintegrated cells is not yet forthcoming. Further investigations on the subject, especially on the differentiation by means of Winkler's oxydase reaction are under way.

#### CLINICAL OBSERVATIONS ON THE EARLY DIAGNOSIS OF MEASLES

It has become easy to recognize measles one day before the eruption of Koplik's spots. The advance gained through this was diagnostically extraordinarily important, but still insufficient for an effective prophylaxis. Then although Koplik's spots are specific for measles they do not always come even three days before the eruption, not frequently they appear only one day before and sometimes simultaneously with the



eruption. And even when they come longer ahead they show only that measles are about to break out. At this stage the disease is already very infectious.

The same sign is of value also for the "conjunctival Koplik" described by Von Schick: Whitish, somewhat prominent spots on the swollen membrane of the caruncula lacrymalis, which, according to Escherich, at times are already visible before the eruption in the mouth.

According to the observations of Jacobson and Baltaceame, Koplik's spots are absent in 9 per cent. of cases, but the author believes that in these cases the phenomenon had already disappeared at the time of the investigation. Out of 130 cases with Koplik, in 105 the end of the first coming on of this symptom could be followed, and it appears that the spots were visible,

In 71 cases	67 per cent.	simultaneously with eruption.
In 18 cases	17 per cent.	2 days before eruption.
In 5 cases	5 per cent.	3 days before eruption.
In 6 cases	6 per cent.	4 days before eruption.
In 4 cases	4 per cent.	5 days before eruption.
In 1 case	1 per cent.	6 days before eruption.
On an average 0.9 of a day before the eruption.		

My observations give the following results for the appearance of Koplik's spots:

	2 times with the eruption.
	6 times 1 day before eruption.
	4 times 2 days before eruption.
	2 times 3 days before eruption.
On an average of	1½ days before eruption.

At times Koplik's spots come on without any eruption or any disease following. In such a case Von Sperk calls it a doubtful case of measles; in one case of mine no further symptom followed. The spots were so characteristic that we all took for granted that the attack of measles was absolutely determined.

If Koplik's sign, then — except in a few cases — is a pathognomonic, early symptom of measles, so the significance of the blood diagnosis is also, without any further symptom, if one can find out the exact commencement of both symptoms — Koplik and blood formation. In my cases on an average there appeared:

Koplik's symptom	1½ days before eruption.
Leukopenia	4.4 days before eruption.
Relative lymphocyte precipitation	6 days before eruption.
Displacement of blood formation	4 days before eruption.
Eosinopenia	2.9 days before eruption.

Moreover, it is true that the last four symptoms could be determined still earlier by means of a reasonable investigation of the circumstances.

Of the remaining early symptoms of measles, we have still to mention the decrease of weight, about 100 gm., found by Von Meunier, which can

be explained by no disturbance of digestion; further, there is an inexplicable increase in temperature.

The question of temperature in incubation was found in two cases important through the whole incubation time; in one case for ten days and in one four days. One case it was observed five days before. In all cases the temperature showed deviation from normal.

Under the circumstance the behavior of the temperature is unquestionably important for diagnosis.

Even if an early recognition and localization of measles in many cases is not so important because of the harmless character of the disease, still its prevention is necessary with all children who may be at all endangered through measles; also with cases of latent tuberculosis, and with frail and anemic children; with those who have a special disposition to disease of the ears, of the heart or of the lungs. In such cases a measles infection may affect the whole life; and nothing is sadder for such children than the common saying that "all children have to have measles."

With regard to the remaining clinical changes in children in the first period of incubation, we find very little in the literature. Heubner finds certain deviations from normal; sometimes cold in the head, slight conjunctival catarrh, coughing, a swollen appearance, watery eyes; these symptoms cease and then the real illness comes on with fever and catarrhal manifestations.

Certain premonitory symptoms were evident in some cases. With Marie, conjunctivitis and reddening of the buccal mucous membranes, six days before the eruption; with Eddy, restlessness and great bedwetting three days before.

#### DURATION OF INCUBATION

The whole incubation period is usually thirteen to fourteen days. Sometimes it exceeds this. Some cases have shown seventeen days and one twenty-one.

#### THE QUESTION OF MEASLES CONTAGION IN FAMILIES

According to Von Abels and others, affinity to measles poison differs according to constitution. This homogeneous behavior of measles in families I find further support for. Pairs of brothers and sisters show a noteworthy parallelism in the cessation of certain symptoms. Next to be noticed is the homogeneity in the time of Koplik's spots before the eruptions.

In the case of three children in the same family, two had Koplik's spots one day before the outbreak; the third at the time of the outbreak, also with all three the interval between both phenomena was very small. My researches also point to a homogeneous capability for reaction with regard to measles virus in families. The two sisters, Ingebord and Hilda D., offered still further agreement. Just as the premonitory

increase of mononuclear neutrophils and the later disappearance of these happened with them on the same day, so the contrary displacement on the right side to the disfavor of polynuclear neutrophils came at the end of the incubation. Also they both had an abnormally long incubation time. Another pair of children, seven months after typical measles, had a perfectly developed second attack.

In a glance over the results of preceding researches, the investigation comes near to becoming an ordinary biological examination; something on the subject of disintegration of cells and their appearance in the blood, on the part of different cell forms in distinct phases of infection, on their place in the protection of the body structure, on the old and the biological value of mononuclear and polynuclear neutrophils, on the meaning of the leukocytic structure on the struggle against infectious virus, etc.

Inasmuch as such speculations, if they are not extremely clear, only complicate matters, and as my object was to bring all possible material to bear on a period of disease hitherto little studied, so I had to give here a long theoretical discussion. For this reason I have not taken up one form of cells — the great mononuclears and transition cells.

These are my results:

1. The rôle of neutrophils and lymphocytes in the understanding of leukocytosis. Ziegler and Schlect understand by leukocytosis "a quantitative cell displacement of white blood-cells in the disfavor of polymorphonuclear (neutrophil) leukocytes. It is connected with a very strong absolute increase of this kind of cell. The lymphocytes can possess normal value, but mostly, at the beginning of leukocytosis, are decreased." I cannot agree with them. In my cases, leukocytosis was much more evident during increase of lymphocytes.

Lymphocytes do not figure in measles as a passive (inactive) element; their absolute fluctuations are throughout greater than those of neutrophils.

2. I should like to recall the statement of Von Pirquet, according to which a hitherto positive cutaneous tuberculin reaction disappears in the course of measles, to become marked again after a week. The cessation of the capability for reaction happens on the last days of the incubation (one, three and five days before the outbreak of the eruption). Von Pirquet explains this phenomenon by an absorption of "ergines," that is, that these bodies act as antibodies, which the clinical reaction interposes between cells and tuberculin. With this disappearance of specific tuberculous antibodies is connected the frequent outbreak of tuberculosis after measles.

It remains to explain the parallelism between these observations and my results with regard to the white blood-corpuscles. Directly toward the end of the incubation time, a decided reduction of the stability of lympho-



cytes takes place, so that a connection between this and the cessation of tuberculin reaction is evident. In tuberculosis, as we well know, there is an entirely distinct significance attached to lymphocytes. Their exclusive or preponderant presence in an exudate or transudate is a direct sign of tuberculosis. So the conclusion seems justified that the lymphocytes stand in a very close relation to the specific tuberculous antibodies, of which they are perhaps the source or carriers.

3. I should like to endorse the explanation first put forward by Von Pirquet in regard to variola; that we have before us in infectious diseases, as it were, "specific reaction diseases" whose nature is to be recognized by a specific reaction of infiltrated antigens with certain antibodies formed from the organism. When the formation of antibodies from the virus (antigen) irritant ceases, then no reaction comes, and no disease. In the serum disease of first infection we have the spectacle of a reaction disease, in which the antigen meets with a virginal organism, and this first induces the formation of antibodies, while in serum disease of reinfection the antigen finds the material necessary to reaction already in the organism. While in the latter case the reaction disease starts in strongly or is hastened, in the former case there is a long period without any symptoms, which goes on from the entrance of the antigen till the formation of the specific reaction body — incubation. And after this there is first an illness of many days. The infectious diseases correspond with the first type (serum disease of first infection).

In measles it is very noticeable that it appears like a kind of specific reaction sickness, but there is not yet proof of it (Von Pirquet, 1907). The resemblance of the appearance of measles and serum sickness of first infection is far-reaching. Long incubation, in serum sickness, eight to twelve days, in measles twelve to seventeen days; then sudden onset of illness with fever and a spotty eruption, which in serum sickness breaks out from the place of injection; in measles from mouth and throat over the body.

The effort to establish measles as a specific reaction sickness (of the type of first infection) received a two-fold benefit from my observations; first, the establishment of leukopenia in measles, according to the researches of Bienenfeld, as also characteristic for serum disease of first infection; and second, the appearances familiar in measles and already described seem to be true also in serum sickness. So Moro finds that the constitutional predisposition with serum sickness of first infection plays a great part.

It remains to be found whether after measles, as after vaccination, a specific hypersensitiveness comes on. Measles very seldom occurs twice, and I don't know whether it is due to a shortening of incubation time in such cases or to a specially violent form of the disease.



## RESULTS

The blood of children with measles shows not only through the eruption, but also in the last of the incubation period certain typical changes, which, inasmuch as they precede the symptoms hitherto acknowledged as early (Koplik, exanthem) by from two to six days, make possible a decidedly earlier diagnosis in suspected cases. These changes are:

1. Leukopenia.
2. Relative and absolute disappearances of lymphocytes.
3. Displacement of Arneth's blood formula on the left side.
4. Decrease of eosinophil cells.

Leukopenia is very marked and on an average noticeable four and a half days before the outbreak, three and three-tenths days before Koplik's spots; two or three days before the eruption leukopenia was at times interrupted by increase of leukocytes.

The disappearance of leukocytes depends on a reversal of the relation between lymphocytes and neutrophils. The lymphocytes, which preponderate in young children, fall away markedly, so that the neutrophils are in excess. This phenomenon appears earlier than leukopenia; on an average, six days before the eruption; four days before Koplik's spots.

The relative lessening of lymphocytes means, reckoned absolutely, not so much an increase of neutrophils, but a disappearance of lymphocytes.

Leukopenia during incubation is caused chiefly through a loss of lymphocytes, next in less degree by a disappearance of neutrophils.

The percentage of mononuclear neutrophils increases toward the end of the incubation. The displacement on the left side of Arneth's blood formula begins on an average of four days before the eruption, two and four-tenths days before Koplik's spots.

The relative increase of mononuclear neutrophils is conditioned sometimes by the increase of mononuclears, sometimes by the reduction of polynuclears.

The eosinophil cells disappear during the eruption and show a decrease even in the incubation, which begins usually two and nine-tenths days before the eruption. During incubation a decided and periodic variation in the breaking up of leukocytes takes place, in which all stages of disintegration cannot be followed. The typical behavior of these disintegration cells, according to their number and kind, cannot be determined.

The body temperature shows even in the early stages of incubation fluctuation and increase.

The understanding of measles as a specific reaction disease of the type of serum disease lies in the understanding of leukopenia and the constitutional reaction.

Leukocytosis is not always identical with neutrophilocytosis, but can also be the expression of lymphocytosis.

Lymphocytes stand in close relation to the specific tuberculous antibodies (the "ergines" of Von Pirquet) of which they are evidently the vehicle.

#### AUTHOR'S CONFIRMATION OF HECKER'S WORK

During the past year at the Children's Hospital of the Boston Dispensary I have had an opportunity to follow Hecker's line of investigation of the blood-picture in the prodromal stage in two different small ward epidemics. The results of which are given in a separate article. My findings concur with those of Hecker.

During the last year a very interesting and instructive article has appeared from the pen of C. Von Pirquet,<sup>4</sup> who takes up the topographical appearance of the eruption and gives many very carefully worked out diagrams of the progress of the eruption from area to area on the body. It would be impossible to give a complete survey of the paper without giving it in whole, but his conclusions are most admirably worked up and are given practically in full, as follows:

#### CONCLUSIONS FROM VON PIRQUET

I assume then that the measles eruption is analogous to small-pox in its explanation; through the agglutinating action of the antibodies on the measles virus, whereby there appears only a toxic reaction on the skin, not a new development of the virus.

Are the observed facts in accordance with the hypothesis? Through observation we have established the following facts:

1. The breaking out on the outer skin starts from the head to the trunk and from there to the extremities.
2. Parts of the body are infected later, according as they are removed from the head and trunk.
3. At the same time certain regions remain retarded in their development of infection; they are the cheeks, knees, nates, and especially the outsides of the elbows.
4. The eruption exhausts itself frequently without having reached the periphery and especially the retarded regions.
5. Hyperemic parts of the skin — red scars, tuberculin reactions, eczema, etc. — hold the eruption more fully and freely; anemic parts (white scars) later and less than the surrounding regions.
6. Also through artificial hyperemia the local eruption can be increased if the hyperemia takes place at least one day before the beginning of the eruption.
7. In the same way can a premature settled congestion cause a retardation of the eruption.

4. Von Pirquet, C. Frhr: Das Bild der Masern auf der ausseren Haut, Wien. Ztschr. f. Kinderh., vi, 1-226.

All these facts accord with each other in showing that an absorption by the tissues with the virus coming by way of the blood-vessels is necessary to the beginning of the eruption. It is not yet clear whether the localization follows through a primary fixing of the measles virus or whether the antibodies must first be absorbed by the tissues in order to fix the measles virus.

I have already pointed out that I do not believe that the exciting causes of infection, as such, generate the eruption embolically, but that it first becomes induced through impregnation of tissue with antibodies that fix themselves in the skin. Let us assume that the antibody production begins about seven days after the infection, that these elements are cultivated chiefly in the large glands and in the marrow of the bones, and from there extend about ten days after the infection through the venous blood and lymph into the circulation.

In this way the arterial blood comes to carry antibodies and give them out gradually into the tissues in the same way as it gives out oxygen. The tissues, which, like the membranes of the nose, larynx and mouth, are very abundantly filled with blood, can be so impregnated in from one to two days, that in them follows an agglutination of the circulating exciting causes of measles. The agglutination brings about a mechanical stop of the exciters in the capillaries which have all been formed into globules and in their place follows the formation of apotoxin, which shows itself clinically as the eruption.

The outer skin is less filled with blood than the membranes are, it is impregnated first from three to four days later. The infection appears earliest in those parts which are nearest the great blood-vessels. When the nearest tissues have absorbed antibodies in sufficient quantity they permit also the impregnation of the peripheral parts. The less blood supports a part of the skin, the farther it is removed from the heart and the longer way the blood has to go through the little blood-vessels, the later follows the impregnation.

The agglutination and the resultant development of the eruption appear according to the proportion of the impregnation by coming out gradually. Between the agglutination and the fixation of the exciter of the eruption and the origin of the clinically perceivable eruption, we have, after the analogy of variola, a period of one to two days.

Let us seek to analyze our further observations on the foundations of this hypothesis.

The effect of hyperemia on a certain part of the skin is easy to understand; through an intertrigo, a tuberculin place, a hyperemic scar streams more blood than through the surrounding skin: therefore, quicker impregnation and freer eruption follows there.

Experimental hyperemia works in the same way (a mustard plaster). But it may be accomplished two days before the beginning of the eruption



and at a time when the agglutination is already past. Congestion retards and condenses the eruption. Through the small arteries in the congested parts the extension of infection follows more slowly. The condensation is perhaps to be attributed to the presence of more exciting causes of infection which are held back by congestion.

This appears to me to be a phenomenon dependent on the number of exciting causes of infection, as we can always observe the modification of an eruption, at first intensive, when it reaches the lower parts of the body.

At times the attack proceeds, as an exception to this, from the head to the feet in the same intensity. Commonly, it is the case that on the second or third day an increase follows on the head and breast, but this time the breaking out on the extremities is not increased over what it first was. The parts to show the infection last show it faintly, transiently or not at all.

I figure it out as follows: The exciting cause spreads through the blood in greater quantity after the incubation time. In the impregnated tissues there is more and more agglutination which produces a constant diminution of the infection. The agglutination involves from day to day less material; the eruption becomes smaller; as a result, more transient, for it acts as an apotoxic reaction until the virus of measles is entirely used up and the impregnation of further tissues (skin of the foot and elbows) causes no more visible phenomena.

With the disappearance of the excitors out of the circulation, the development of apotoxin in the central organs ceases; with the increase of the eruption, formation of apotoxin takes place.

The accompanying table (Table 13) shows these phases one by one in their time relation and succession.

In contrast to the scarce and insufficient treatment in the literature, the effort has here been made for the first time to study the development of measles in the outer skin fully and with sufficient material.

As far as I know, it is absolutely the first time that an acute eruption has been registered in as satisfactory a way and a systematic explanation undertaken.

After different attempts to present the eruption through photographs and drawings, a definite method of schematic drawing was chosen, and I drew designs for each day of the eruption in forty-six cases of measles.

Among these were ten cases chosen in which the earliest beginning of the eruption had been observed already, and in them the advance of the eruption and the course of the first day studied.

The later course and the cessation of the eruption were worked up in nine cases, which had drawings made of the eruption from the second to the fifth day. These and all the remaining cases were used in answer to questions on the subject.



TABLE 13.—PHENOMENA OF THE ERUPTION OF MEASLES

Time	Exciter	Antibodies	Following the Coming Together of Exciters and Antibodies	Clinical Appearances
Days before eruption.. 14	Take hold in the body (infection).			
14-4	Gradual increase.			
4	.....	Beginning of appearance in circulation.	Formation of apotoxin.	Fever.
3	Diminution of gradual ag- glutination and digestion (through the antibodies.	Impregnation of mem- branes of respiration.	Agglutination in respira- tion membrane.	Coughing, sneezing, eruption
2	.....	And mouth membrane.	Agglutination in mouth membrane.	Koplik's spots.
1	.....	Impregnation of skin on head and back.	Agglutination begins in outer skin.	Eruption begins on head and back.
Eruption begins..... 0	.....	Impregnation of skin on trunk and along the large vessels.		
Day after eruption..... 1	Smaller residue.	Impregnation of extremi- ties, nates.	Agglutination on trunk. etc.	Eruption on trunk, and in- side of arms and thigh.
2	Entirely agglutinated.	Impregnation on feet and elbow.	No agglutination because the exciters cease. Apo- toxin formation ceases.	The ends of extremities re- main free, fever ceases.

## FIRST SIGNS OF MEASLES ERUPTION

The facts we have established apply to the beginning of the eruption.

This takes the form of scattered red papules on the head and trunk, and it appears in different regions in the following order of intensity:

Behind the ears.

In the middle of the upper sections of the back.

In the region of the mouth and nose.

On the cheeks and in front of the ears.

On the forehead.

Seldom and sparsely on the breast and abdomen.

## THE ERUPTION AT THE BEGINNING OF THE SECOND DAY

The eruption now spreads to the rest of the body in the course of from two to four days; on an average in three days.

After the course of the first twenty-four hours the average development of the eruption is as follows:

On the head and back region there is a plentiful eruption; this covers the upper and middle parts only. The cheeks are slightly affected and show little or no eruption.

The eruption is slight on the breast, abdomen, shoulders and in the axilla.

The beginning of the breaking out on the other parts of the arm, the thigh, the popliteal space, the nates and front of the leg shows the papules like tents joined together.

The back surfaces of the leg, the feet, the knees and elbows are still free.

## THE ERUPTION AT THE BEGINNING OF THE THIRD DAY

After forty-eight hours, progress is either ended or is still in the above-described stage. On the average, it has the following extension:

Head, trunk, shoulders, the anterior surfaces of the upper arms and the thighs are thoroughly covered.

Less constantly the eruption appears on the posterior surface of the upper arm, the forearm and the back of the thigh; slight eruption shows on the popliteal space, the legs, less on the hands and knees, and never on the nates. The eruption begins on the feet, while the elbows are still usually free.

## THE ERUPTION ON THE FOURTH AND FIFTH DAYS

On an average the eruption is now fully developed, only the nates, feet and elbows are often backward in showing it. The fifth day only exceptionally brings a more thorough breaking out, which shows itself by appearing on a region hitherto free or by becoming more violent on a region hitherto only faintly affected.

# HOW THE ERUPTION LOSES COLOR

The attack is very red in its first appearance, but after one to two days the hyperemia diminishes; it leaves behind at the same time a light pigmentation.

This process of fading begins usually on the forehead where the eruption is accustomed to lose in intensity at the beginning of the second day.

At the beginning of the third day on the average, the forehead and scalp are entirely faded; the commencement of fading shows itself in other places, on the trunk and shoulders.

At the beginning of the fourth day the fading has begun on the extremities; on the forehead and scalp also the slight pigmentation has usually entirely disappeared.

At the beginning of the fifth day, finally, the whole head (with the exception of the cheeks) has entirely lost the eruption; while the pigmentation is still plain on the other parts of the body so far as there was eruption.

The elbows and feet remain entirely exempt from such eruption, more seldom the knees, nates and hands.

## THE DURATION AND FORM OF A SINGLE EFFLORESCENCE

For its full development (from the first appearance of the papule to the disappearance of the hyperemia) the eruption takes on an average of three days; the latest in coming (i. e., on nates and feet) have a quick cessation; they are paler, more transient, disappear often without any pigmentation.

A single efflorescence begins mostly as the smallest red follicular elevation and are often surrounded with enemic spots; they enlarge on all sides joining with adjacent efflorescences, and then can so cover the skin that only few clear unaffected spots of normal skin remain. Besides this, there is also on the first day an increase of new papules which develop themselves — after a short time their hyperemia commonly again disappears and leaves behind pigmentation.

The intensity of the starting of new papules and the increase of the eruption diminishes very much after the third day.

It amounts to in units:

First Day	Second Day	Third Day	Fourth Day
172	160	87	17

## THE INFLUX OF THE ERUPTION AS DEPENDENT ON COMMON AND LOCAL CONDITIONS

Commonly the influx can only be obscurely understood in its influence at the cessation of the eruption. In summer, the attack appears to develop more quickly than in winter. With little children the eruption

is frequently more incomplete than with larger ones. Brothers and sisters show extraordinary similarity in the character of the eruption.

The influence of local causes on the ending of the eruption is very great. The attack is more violent on all chronically hyperemic places than on the normal skin surrounding them, equally whether the hyperemia has been brought on by tuberculin, pressure of garters or intertrigo. Localized multiform erythema and urticaria on the extremities present before the measles tends to bring on a very thorough eruption which the extremities develop sooner than the trunk.

Artificial inducing of the eruption was reached once by the application of irritation and by congestion, but only when this hyperemia was brought about at the latest one day before the appearance of the eruption.

#### THE CONNECTION OF THE ERUPTION WITH THE DISTRIBUTION OF ARTERIES AND THE LENGTH OF AN ARTERY IN ANY PART OF THE SKIN

We tried to discover the cause of the cessation of the measles eruption which usually we observed was related to the distribution of the great nerves and arteries.

The sensory nerves have a different distribution from the eruption; a stopping of the eruption corresponding with the "Headschen" zones would follow an entirely different rule. The eruption cannot, therefore, be brought into connection with the distribution of the sensory nerves.

There is a kind of correspondence with the course of the great arteries. The course of the eruption follows the rule — with the exception of one point not yet cleared up — that it appears the sooner according as the part of the skin is nearer the arterial system, and the nearer it lies to the great vessels and the more circulation there is.

The eruption comes on later according as the region of the skin is far from the heart and according as the blood has a longer way to pass through the vessels and according as there is less hyperemia.

#### HYPOTHESIS WITH REGARD TO THE NATURE OF THE MEASLES ERUPTION

From the basis of the observed facts and from correspondence with the conditions in variola and vaccines, the hypothesis has been reached that the eruption comes on from an apotoxic reaction on the exciting causes of measles which have gotten a hold in the capillaries.

As the cause of fixation, we may hypothetically assume that there is an agglutination which the measles virus undergoes when it passes through the capillaries.

The impregnation of the outer skin with antibodies may be the cause of the origin of the eruption. This impregnation follows after a manner as oxygen is given of arterial blood. In this way the cessation of the eruption may be explained: First, those regions are impregnated which



have a very intensive circulation (mucous membranes) or the parts which lie near the heart and the great blood-vessels. After these become impregnated, then the remaining parts take up successively enough antibodies to bring about an agglutination of the exciting causes of measles.

Through the agglutination the exciting cause is spread gradually through the circulation; the agglutination finds much less material in the regions later impregnated (the extremities); so the eruption here is much slighter and more fleeting. The frequent freedom from eruption of the elbows, feet and nates is explained thus, that at that time when the parts of the skin least provided with arteries are impregnated, no exciting causes of measles are at that moment in the blood.

This series of articles on the study of measles is most interesting and instructive, and should lead to renewed efforts toward finding the etiological factor more positively than it is at present. The immunity reactions going on in the body during the incubation period of measles are most definite and it should be possible to put them to some diagnostic use by working out some definite early reactions.

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## INDEX TO VOLUME VI

	PAGE
Acker, George N.: Parotitis complicated with meningitis.....	399
Atmospheric conditions, influence of, on the mortality of infants suffering with gastro-intestinal disorders.....	319
Bacillus abortus. Experiment with raw and heated cow's milk and its lesson, children and infants .....	326
Bacillus abortus. Experiment with raw and heated cow's milk and its lesson, with comments on B. abortus.....	334
Bierring, Walter L.: Status thymolymphaticus with report of four cases in one family .....	75
Blackader, A. D.: Mucous cyst of the cecum in an infant ten weeks old, producing obstruction of the ileocecal valve and symptoms simulating an intussusception .....	99
Blackfan, Kenneth D.: A study of the Wassermann reaction in one hundred infants .....	162
Bleyer, A. S.: The influence of atmospheric conditions on the mortality of infants suffering with gastro-intestinal disorders.....	319
Blood of children and infants, complement-fixation reaction of the, using the bacillus abortus as antigen.....	326
Blood: simple syringe transfusion with special cannulas.....	28
Bosworth, A. W.: Casein in infant feeding. Experiments in exact percentages	394
Bowditch, Henry I.: Casein in infant feeding. Experiments in exact percentages .....	394
Brown, Alan: Luetin reactions in infancy .....	171
Brown, Alan: Results with salvarsan in hereditary syphilis.....	174
Campbell, Geo. A.: Results of treatment with salvarsan in late congenital syphilis .....	187
Cardiac disease in childhood, with special reference to prognosis.....	104
Casein in infant feeding. Experiments in exact percentages.....	394
Cecum, mucous cyst of the, in an infant ten weeks old, producing obstruction of the ileocecal valve and symptoms simulating an intussusception.....	99
Circulatory system, résumé on the.....	131
Clark, H. C.: A case of congenital cyst of the thyroid gland, in a child aged 1 year, producing death by asphyxiation.....	408
Clinton, Marshall: The diagnosis of intussusception by x-ray.....	93
Collins, Arthur N.: Urinary lithiasis in infancy.....	245
Complement-fixation reaction of the blood of children and infants, using the Bacillus abortus as antigen.....	326
Cowie, D. M.: A rapid clinical method for the estimation of total fat in infants' stools .....	192
Craster, C. V.: Analysis of one thousand cases of epidemic measles.....	122
Cyst, congenital, of the thyroid gland, a case of, in a child aged 1 year, producing death by asphyxiation .....	408
Dana, Richard T.: Formula for the determination of the surface area of infants .....	33
DeBuys, L. R.: Roentgen ray in pyloric obstruction .....	344
Diarrhea, summer heat and.....	289
Diphtheria, is it frequently a bacteriemia?.....	23
Dunn, Chas. Hunter: Cardiac disease in childhood, with special reference to prognosis .....	104
Duodenal ulcers in infancy .....	381

# INDEX TO VOLUME VI

	PAGE
Dyspituitarism .....	145
Ear, résumé of the literature on the.....	363
Esophagus, occlusion of the, in early life, three types of.....	1
Farmer, Alfred G.: A case of congenital cyst of the thyroid gland, in a child aged 1 year, producing death by asphyxiation .....	408
Fat, total, in infants' stools, a rapid clinical method for the estimation of..	192
Feeding, infant, casein in. Experiments in exact percentages.....	394
Feldstein, Samuel: Résumé of the recent literature on meningitis (not includ- ing meningococcus meningitis) .....	199
Freeman, Rowland G.: The diagnosis and treatment of pyelitis in infancy...	117
Friedlander, Alfred: The diagnosis and treatment of enlarged thymus.....	38
Gastric secretion of infants at birth.....	264
Gastro-intestinal disorders, the influence of atmospheric conditions on the mortality of infants suffering with.....	319
Goodrich, J. A.: Status thymolymphaticus, with report of four cases in one family .....	75
Heart, needle in the, fifteen months; death; autopsy.....	87
Heat and summer diarrhea .....	289
Hecker, R.: Cytological and clinical observations during the incubation period of measles .....	413
Heiman, Henry: Résumé of the recent literature on meningitis (not includ- ing meningococcus meningitis) .....	199
Hess, Alfred F.: The gastric secretion of infants at birth.....	264
Holt, L. Emmett: Duodenal ulcers in infancy .....	381
Holt, L. Emmett: Results with salvarsan in hereditary syphilis.....	174
Holt, L. Emmett: Wassermann reaction in hereditary syphilis, in congenital deformities and in various other conditions in infancy.....	166
Hubbard, W. S.: A rapid clinical method for the estimation of total fat in infants' stools .....	192
Howland, John: A formula for the determination of the surface area of infants .....	33
Index to Current Pediatric Literature.....	57, 137, 215, 285, 372, 440
Intussusception, diagnosis of, by x-ray.....	93
Kyle, D. Braden: Review of the literature on nose and throat with reference to children .....	277
Larson, W. P.: Complement-fixation reaction of the blood of children and infants, using the bacillus abortus as antigen.....	326
LeWald, Leon Theodore: Further study of the anatomy and physiology of the infant stomach based on serial Roentgenograms.....	232
Lewis, D. M.: The cell content of milk.....	225
Lindeman, Edward: Simple syringe transfusion with special cannulas...	28
Lithiasis, urinary, in infancy .....	245
Lucas, William Palmer: A review of recent work on measles.....	412
Luetin reaction in infancy .....	171
Measles, cytological and clinical observations during the incubation period of	413
Measles, epidemic, analysis of one thousand cases of.....	122
Measles, a review of recent work on.....	412
Meningitis, parotitis complicated with.....	399
Meningitis, résumé of the recent literature on (not including meningococcus meningitis) .....	199
Metabolism of the child, the influence of activity on the.....	15
Milk, cow's, raw and heated, an experiment with, and its lesson. With com- ments on bacillus abortus .....	334
Milk, the cell content of.....	225
Mucous cyst of the cecum in an infant ten weeks old, producing obstruction of the ileocecal valve and symptoms simulating an intussusception..	99
Murschhauser, Phil. Hans: The influence of activity on the metabolism of the child .....	15

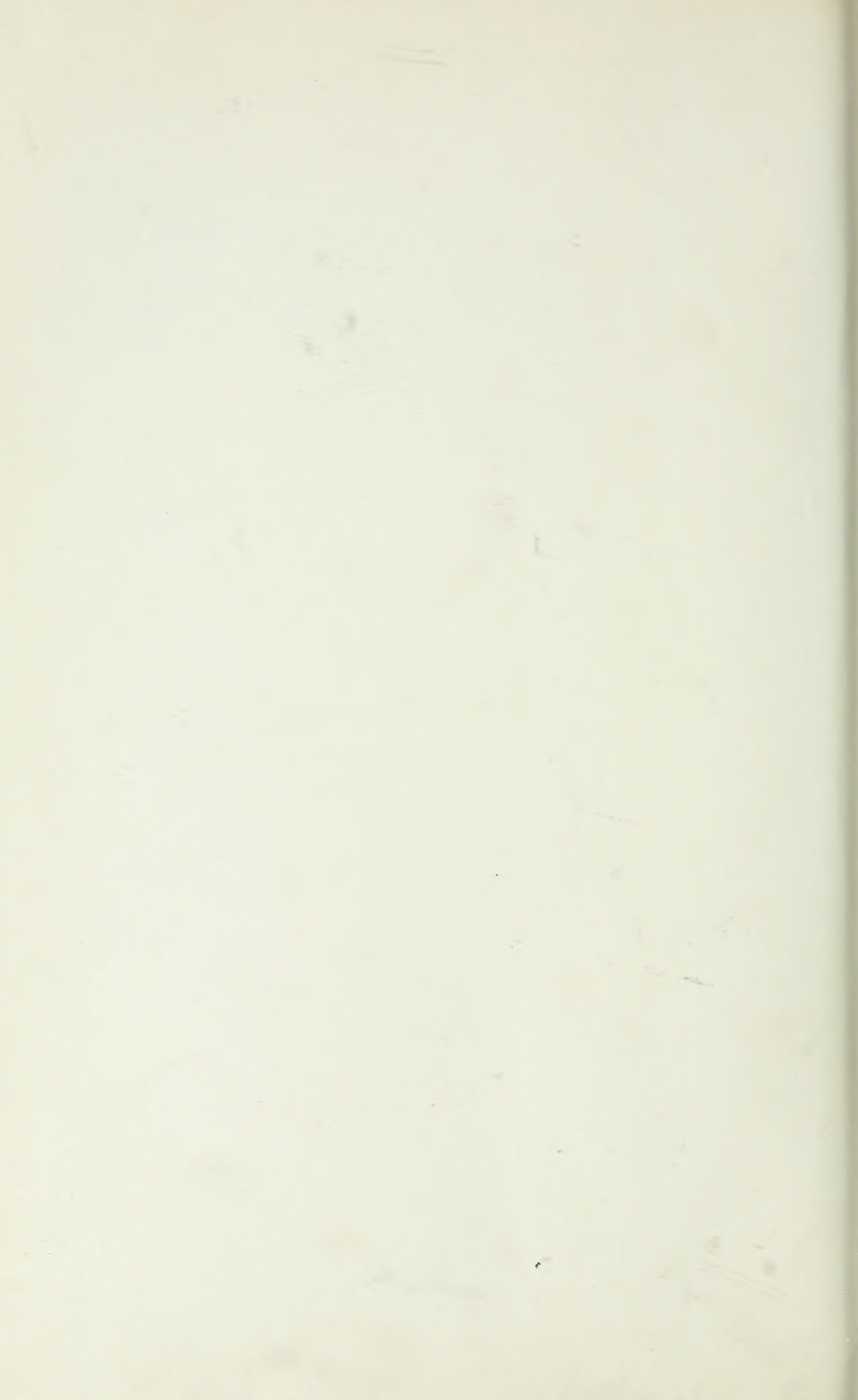


# INDEX TO VOLUME VI

	PAGE
Nicholson, Jr., S. T.: A study of the Wassermann reaction in one hundred infants .....	162
Nicoll, Jr., Matthias: Is diphtheria frequently a bacteriemia?.....	23
Northrup, W. P.: Needle in the heart fifteen months; death; autopsy.....	87
Nose and throat, review of the literature on, with reference to children.....	277
Pancreatic insufficiency .....	65
Parotitis complicated with meningitis .....	399
Pisek, Godfrey R.: The further study of the anatomy and physiology of the infant stomach based on serial roentgenograms.....	232
Porter, Langley: Pancreatic insufficiency .....	65
Pediatrics, progress in.....	38, 131, 199, 277, 363, 412
Pyelitis in infancy, diagnosis and treatment of.....	117
Pyloric obstruction, the Roentgen ray in.....	344
Reuben, Mark S.: Dyspituitarism .....	145
Roentgen ray in pyloric obstruction.....	344
Rotch, Thomas Morgan: Three types of occlusion of the esophagus in early life .....	1
Salvarsan, results of treatment with, in late congenital syphilis.....	187
Salvarsan, results with, in hereditary syphilis.....	174
Schlossmann, Arthur: Influence of activity on the metabolism of the child... ..	15
Schroeder, E. C.: An experiment with raw and heated cow's milk and its lesson. With comments on bacillus abortus.....	334
Sedgwick, J. P.: Complement-fixation reaction of the blood of children and infants, using the bacillus abortus as antigen.....	326
Smith, Richard M.: Vulvovaginitis in children.....	355
Smith, S. Mac Cuen: Résumé of the literature on the ear.....	363
Snow, Irving M.: Diagnosis of intussusception by x-ray.....	93
Status thymolymphaticus, with report of four cases in one family.....	75
Stomach, infant, further study of the anatomy and physiology of, based on serial roentgenograms .....	232
Strathy, Geo. S.: Results of treatment with salvarsan in late congenital syphilis .....	187
Summer diarrhea and heat .....	289
Surface area of infants, a formula for the determination of the.....	33
Syphilis, hereditary, results with salvarsan in.....	174
Syphilis, hereditary, the Wassermann reaction in, in congenital deformities and in various other conditions in infancy.....	166
Syphilis, late congenital, results of treatment with salvarsan in.....	187
Thymus, enlarged, diagnosis and treatment of.....	38
Thyroid gland, case of congenital cyst of, in a child aged 1 year, producing death by asphyxiation .....	408
Transfusion, simple syringe, with special cannulas.....	28
Urinary lithiasis in infancy .....	245
Vulvovaginitis in children .....	355
Wassermann reaction in hereditary syphilis, in congenital deformities and in various other conditions in infancy.....	166
Wassermann reaction in one hundred infants, a study of the.....	162
White, T. Wistar: A study of the Wassermann reaction in one hundred infants .....	162
Wilcox, Harriet, L.: Is diphtheria frequently a bacteriemia?.....	23
Young, J. Herbert: Résumé on the circulatory system.....	131
Zahorsky, John: Heat and summer diarrhea .....	289

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